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Practical Approach to PEDIATRIC INTENSIVE CARE

Praveen Khilnani

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Practical Approach to Pediatric Intensive Care

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Practical Approach to Pediatric Intensive Care

Second Edition

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To my mother

Late Smt Laxmi Devi Khilnani

Who left for heavenly abode on May 2001
She always knew I could do it whenever I thought I couldn't
She was the one who taught me to always be optimistic and hardworking
God will take care of the rest

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Foreword

Pediatric critical care is a relatively new subspecialty and has developed rapidly in many parts of the world. In India, it is still in infancy but over the last few years, it has made great strides. The standard of care for the critically ill or injured child is more or less at par with other countries. It is very gratifying to see that many institutions have excellent PICUs with current state of the art. The Indian Society of Critical Care Medicine and the Indian Academy of Pediatrics are to be commended for their lead and enormous input to disseminate the knowledge and skills to physicians, nurses and other health care personnel. With the explosion in current technology and monitoring techniques, many lives are being saved.

This book entitled *Practical Approach to Pediatric Intensive Care* edited by Dr Praveen Khilnani, Senior Consultant Pediatric Intensivist at Max Hospitals, New Delhi will be a valuable companion to all the medical and nursing personnel. Many areas and topics have been covered well by the author who is well experienced to conditions that prevail the world over.

A book like this cannot be exhaustive and complete. But, it contains practical guidance for the routine daily care of the sick child. I commend the editor for his efforts and venture.

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Preface to the Second Edition

As the field of pediatric critical care continues to grow, newer developments and guidelines have emerged. New resuscitation guidelines as well sepsis guidelines have been included, in addition to overall upgrading of latest information in the field of pediatric critical care. Practice oriented flow charts have been added to several chapters for common PICU problems.

It is hoped that this book will emerge as truly practical companion to any one taking care of a critically ill child.

Praveen Khilnani

Preface to the First Edition

The field of pediatric critical care (pediatric intensive care) is rapidly advancing and new innovations and technologies are being frequently incorporated into the delivery of pediatric critical care. The role of the pediatric critical care specialist (pediatric intensivist) has become more defined as pediatrician who specializes in the field of diagnosis of critical pediatric illnesses and prompt management employing all—the principles of pediatric pathophysiology including hemodynamic disturbances, tissue oxygen delivery, septic process, trauma and surgical stress and systemic inflammatory response syndrome (SIRS). Treatment of critical illness involves a good grasp on ways to improve oxygen delivery for management of shock, respiratory failure and sepsis. Clinical reserve in a pediatric patient is far less compared to an adult patient, therefore, a timely detection of a clinically deteriorating patient as well as prompt institution of appropriate resuscitative efforts goes a long way. A pediatric intensivist must be well trained in emergency procedures such as central line placement, endotracheal intubation, bag mask ventilation, arterial line placement, sedation, ventilator management, chest tube placement, lumbar puncture, oxygen therapy, cardiopulmonary resuscitation, intraosseous line placement and above all the application of appropriate clinical judgement to use the above skills effectively and safely to improve patient outcome.

This book has been written and edited to emphasize practical aspects of pediatric intensive care contributed by various national and international authors involved in routine day-to-day management in the multidisciplinary pediatric intensive care unit with collaboration of a team of specialists including medical, surgical, nursing, and other important ancillary services. Ethical, legal, and nursing issues have also been included. I sincerely hope this book will be a resource to those practicing and training in the field of pediatric critical care medicine.

Effort has been taken to present currently accepted consensus on therapy rather than dogmatic opinions. I wish to thank all the contributors and my family members for their unconditional support.

Praveen Khilnani

Development of Pediatric Critical Care

1889		First infant respirator Egon Braun, Vienna
1910		First positive pressure ventilator
1954		Extracorporal circulation described
1954		First PICU, Goteburg, Sweden Closed chest defibrillation described ECMO described
1957		Severinghaus electrode: led to blood gas analysis
1958		First physician-directed multidisciplinary adult ICU, Baltimore City Hospital
1963		First liver transplant
1964		Theodore Striker, MD, becomes first pediatric critical care fellow, Philadelphia
1967		First US physician-directed PICU, Philadelphia Society of Critical Care Medicine (SCCM) established
1972		First US Textbook of Pediatric Critical Care Clement Smith (Editor)
1973		First edition, Critical Care Medicine (CCM)
1974		Pulse oximetry developed
1982		Pediatric Section of Society of Critical Care Medicine established
1983		First advanced pediatric life support PALS copywritten Formation of section on critical care of AAP
1986		US Guidelines published for pediatric air and ground transport
1987		First Comprehensive Textbook for Pediatric Critical Care—MC Rogers First pediatric critical care board examinations
1988		American College of Critical Care established Prism score described by Murrey Pollack
1989		First pediatric critical care fellowship certified by American College of Graduate Medical Education (ACGME)
1993		US guidelines and levels of care for PICUs published
1993		Indian Society of Critical Care Medicine (ISCCM) established
1993		First Indian Academy of Pediatrics (IAP) intensive care conference, Delhi Manual of pediatric intensive care published—K Chugh and Praveen Khilnani
1997		World congress and establishment of World Federation of Pediatric Intensive Care (WFPICC), Baltimore
1998		IAP intensive care chapter established
1998		1st national congress on pediatric intensive care, Nagpur
2000		ISCCM pediatric section formed
2001	:	IAP and ISCCM PICU guidelines and levels of care published
2002	:	First pediatric critical care fellowship started
2003	:	First pediatric critical care fellowship exam, Surat
2004	**:**	**First comprehensive Indian Textbook on Pediatric Intensive Care: Praveen Khilnani**
2007	**:**	**DNB pediatric critical care started in India.**

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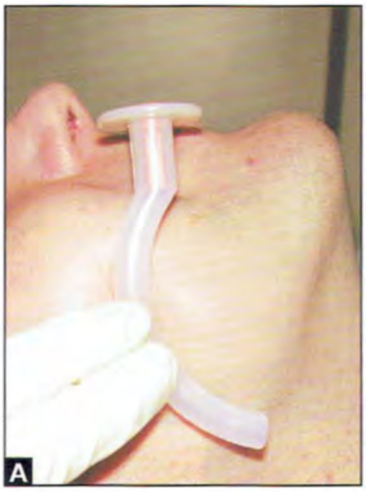


Fig. 4.2A: Correct estimation of size of oral airway (mouth to angle of mandible)

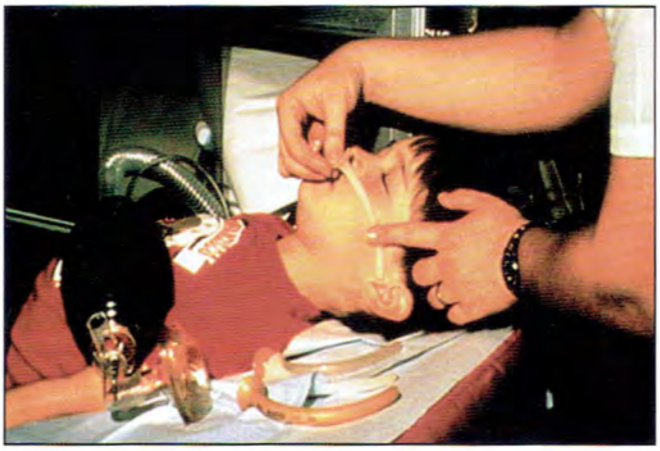


Fig. 4.3: Proper placement of NP airway

Fig. 7.1: Clinical observation of a critical patient by nurse by the bedside in PICU

Fig. 7.2: Human monitoring (Bedside examination has no substitute)

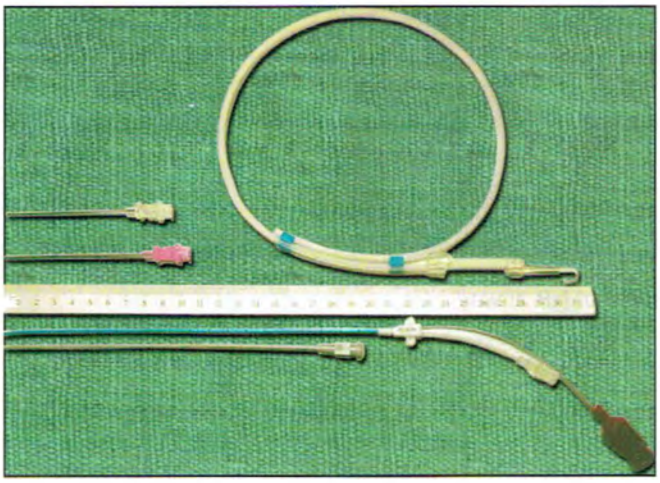


Fig. 7.3: PICCO (Partially invasive pulse contour CO monitoring)

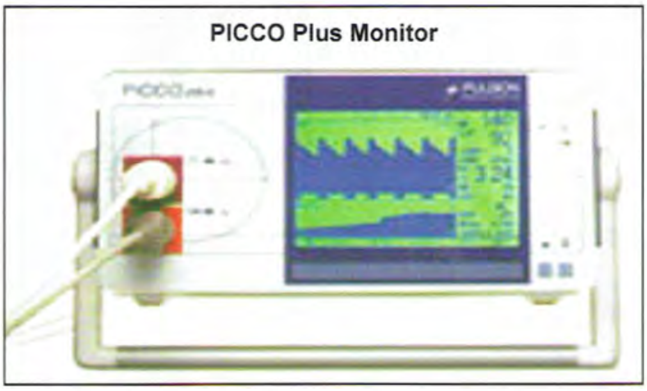


Fig. 7.4: Partially invasive cardiac output monitor

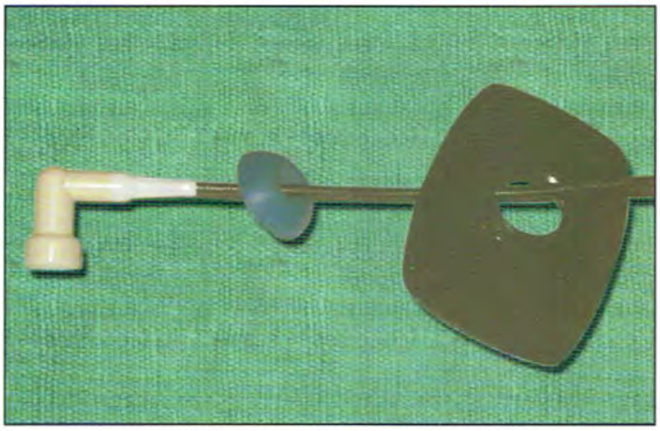
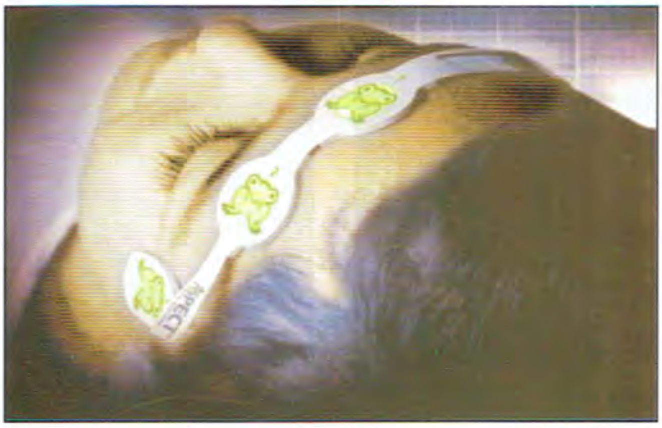
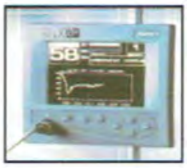


Fig. 7.5: Doppler technique of cardiac output estimation (USOM CO) temperature monitors



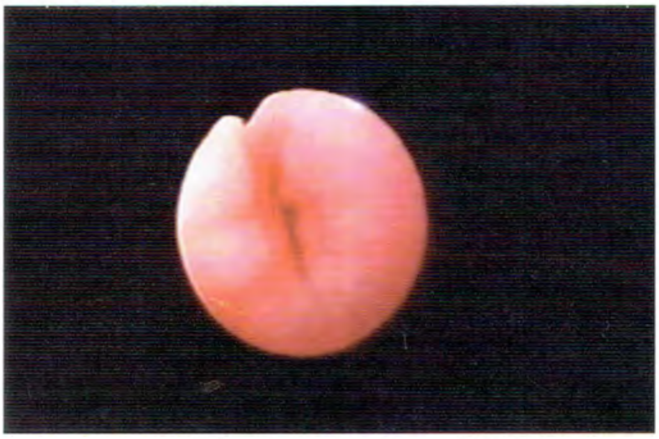
Brain monitoring technology for objective sedation assessment of pediatric patients in the ICU



- Mechanical ventilation
- Neuromuscular blockade
- Barbiturate coma
- Bedside procedures

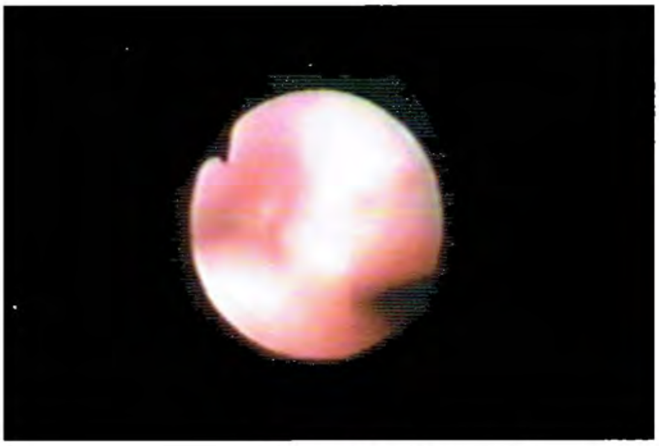
Fig. 7.7: BIS scale in use with monitor

PLATE 4

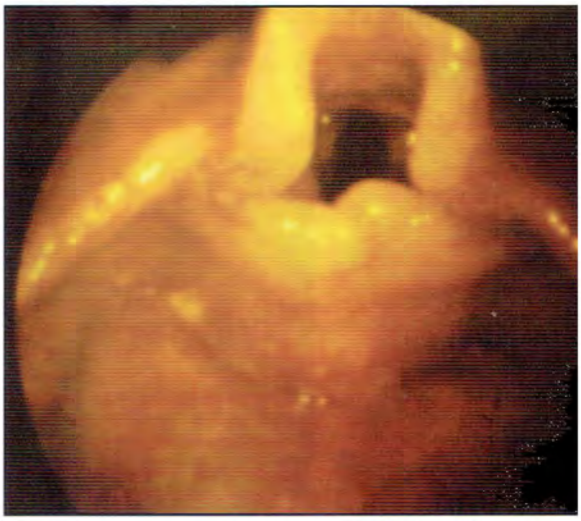


Extrinsic bronchial compression

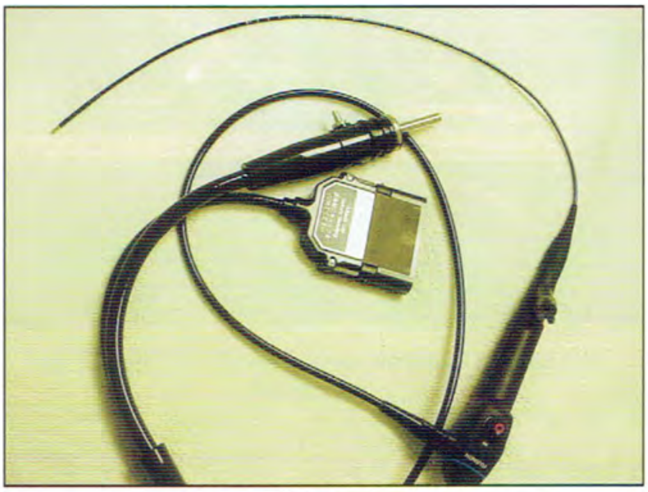
Bronchoscopic videoscope cart



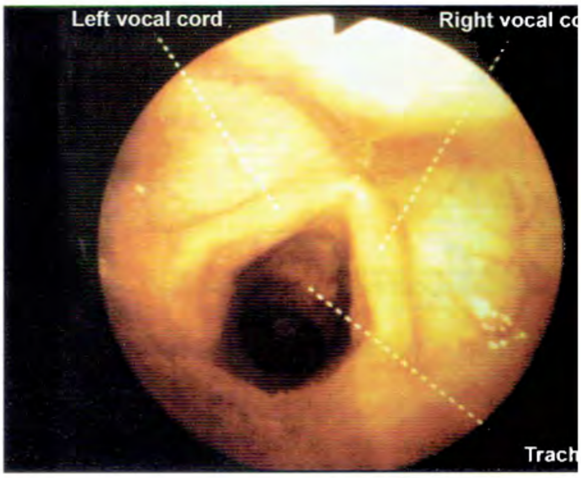
Endobronchial tuberculosis



Bronchoscopic view of larynx



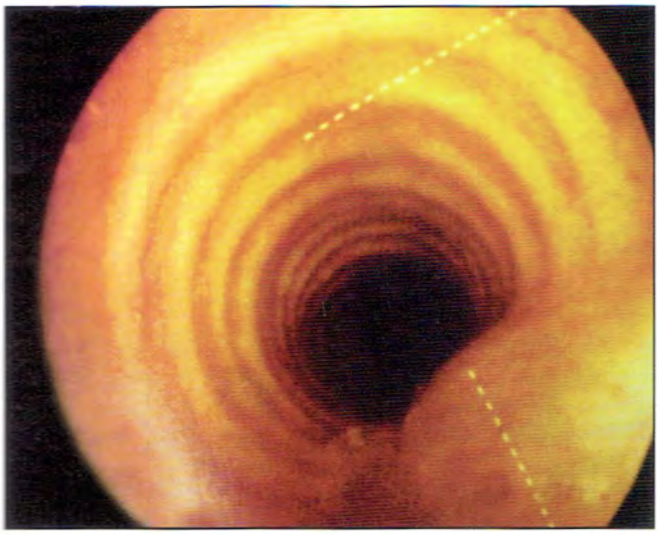
Neonatal bronchoscope



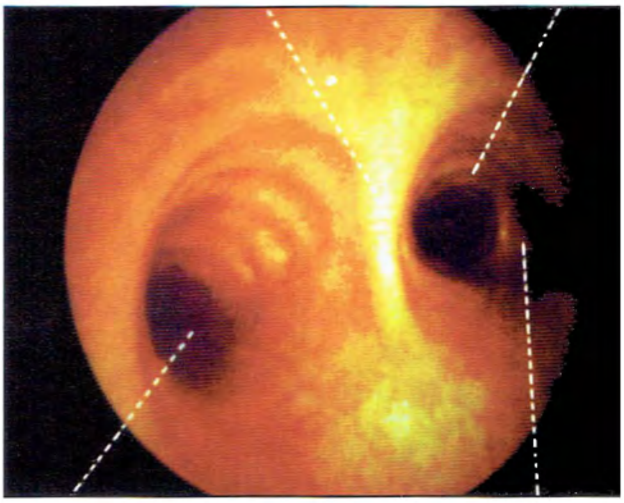
Left vocal cord
Right vocal c
Trach

Bronchoscopic view of vocal cords

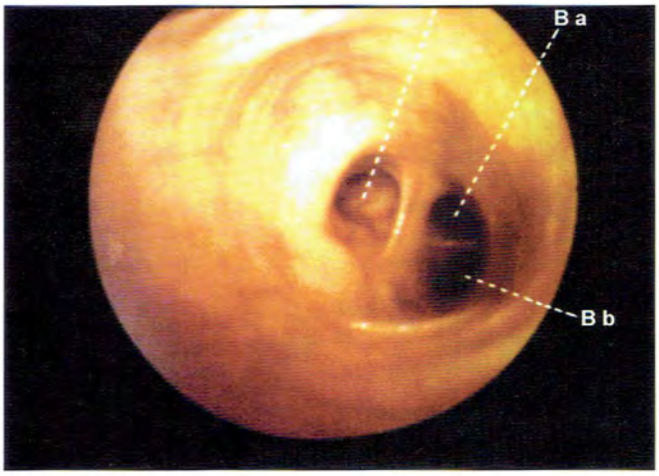
PLATE 5



Tracheal rings



Right mainstem bronchus with right upper lobe take off



Left bronchus

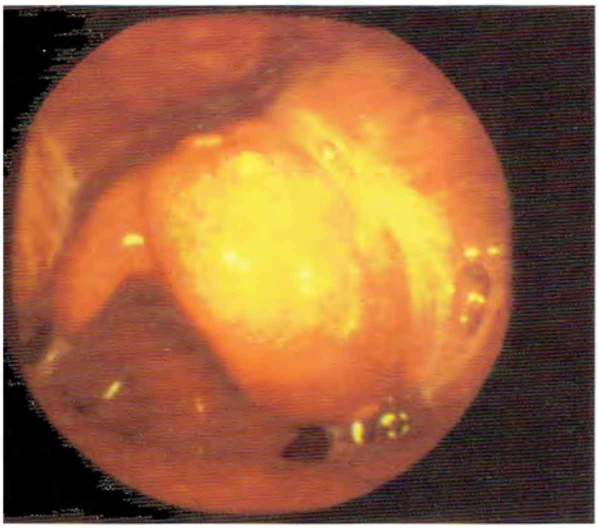


Fig. 18.5: Epiglottitis

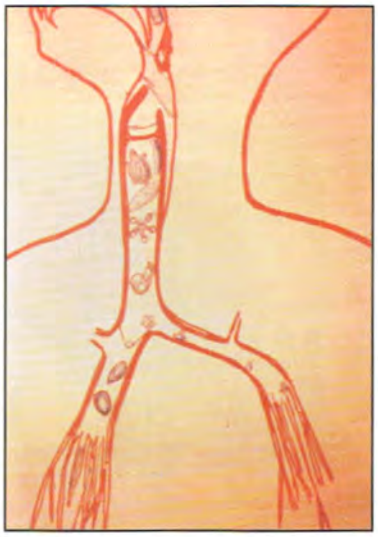


Fig. 18.22: Various foreign bodies in the airway

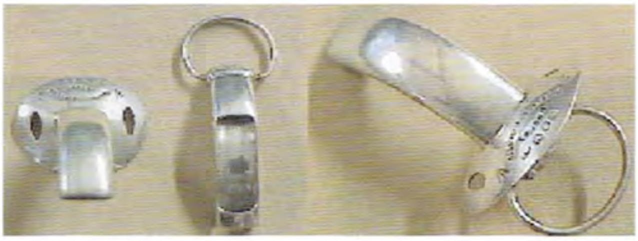


Fig. 21.2: Various pediatric and neonatal tracheostomy tubes

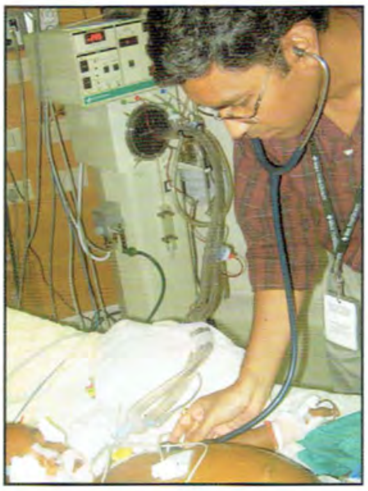


Fig. 27.4: Sensormedics 3100 A oscillator in use

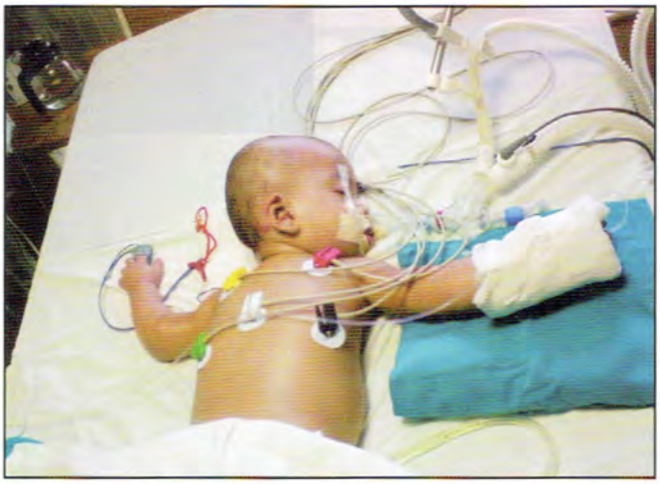


Fig. 27.5: Prone positioning

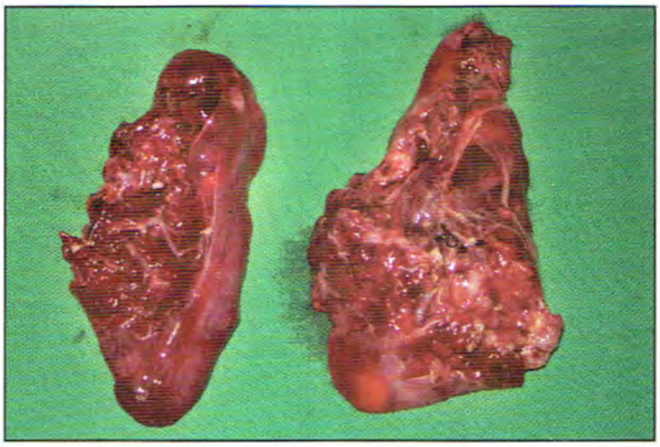


Fig. 31.3: Pathological specimen of lungs with cystic adenomatoid malformation

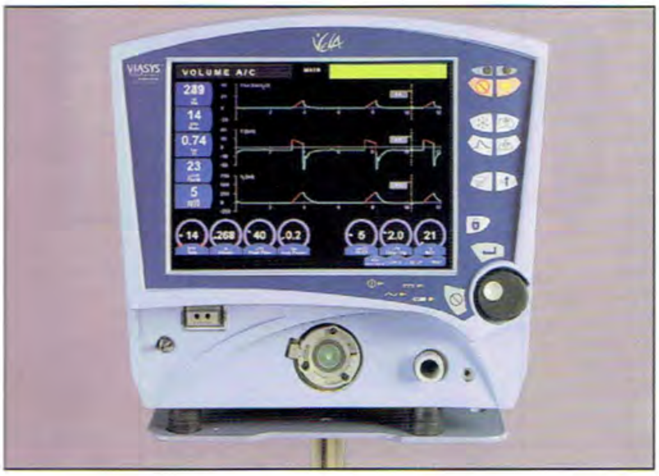


Fig. 35.1: VELA ventilator

Fig. 35.3: Ventilator model AVEA

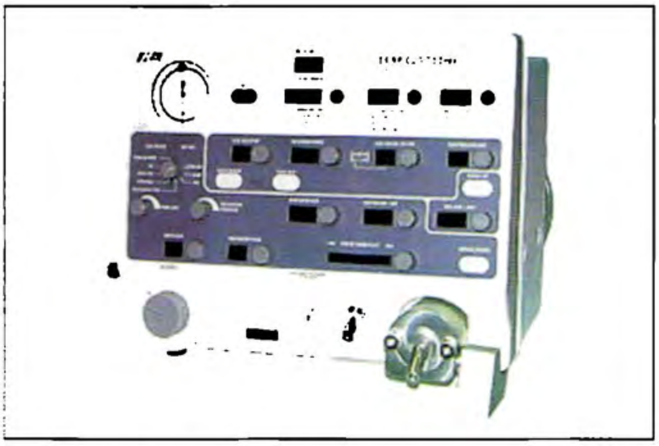


Fig. 35.2: Neonatal ventilator mode bearcub

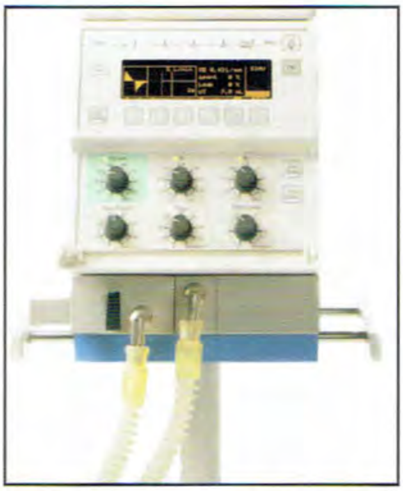


Fig. 35.4: Drager babylog 8000

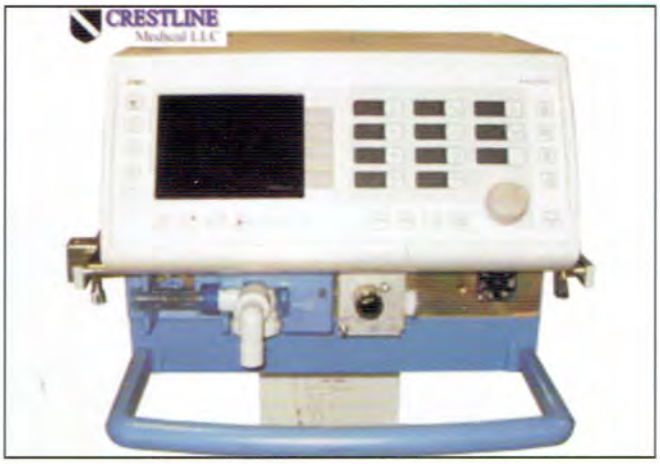


Fig. 35.5: Drager babylog 8000 plus

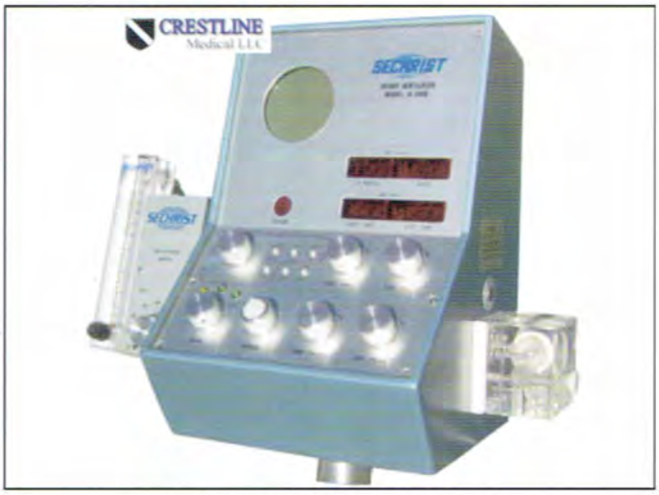


Fig. 35.8: Sechrist ventilator Old

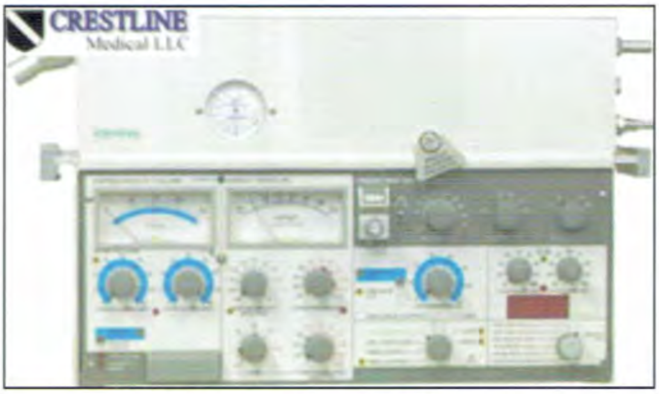


Fig. 35.6: Siemens servo 900C ventilator

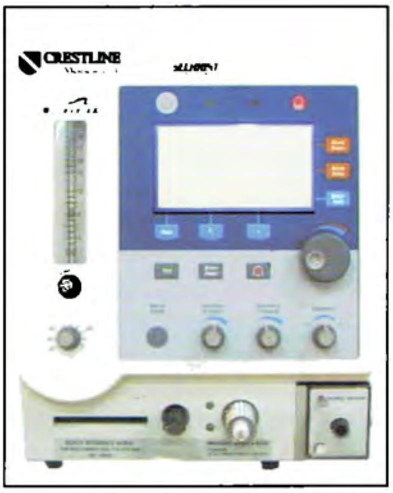


Fig. 35.9: Sechrist Ventilator New

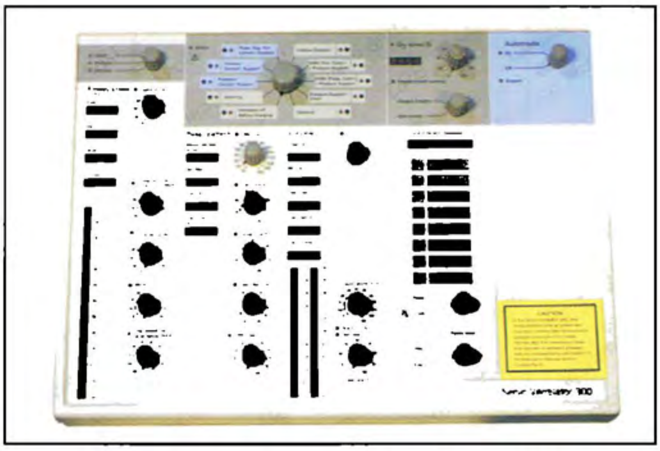


Fig. 35.7: Siemens servo 300/300A ventilator

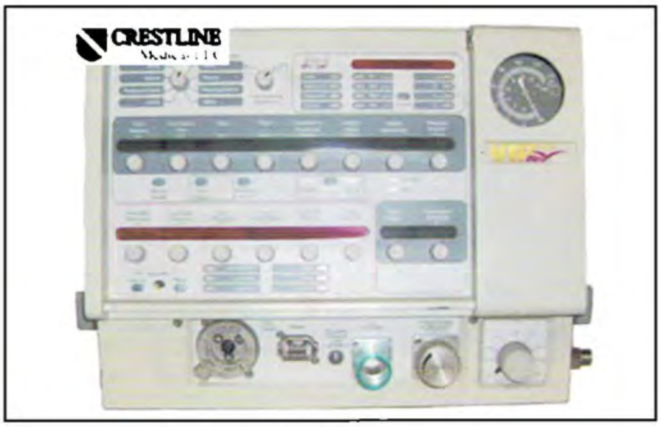


Fig. 35.10: VIP bird ventilators

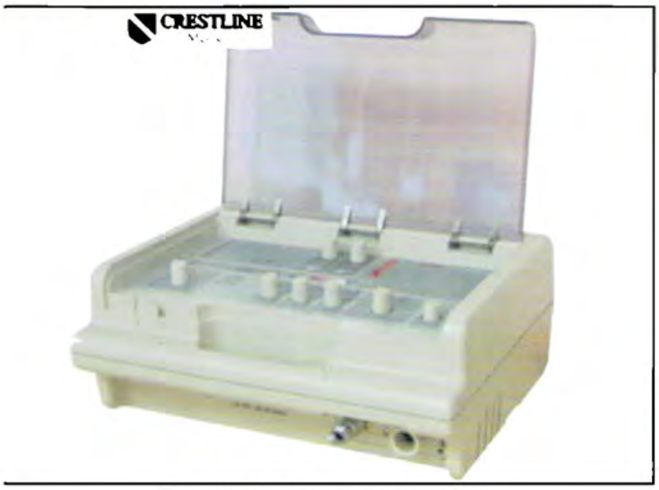


Fig. 35.11: Transport ventilator

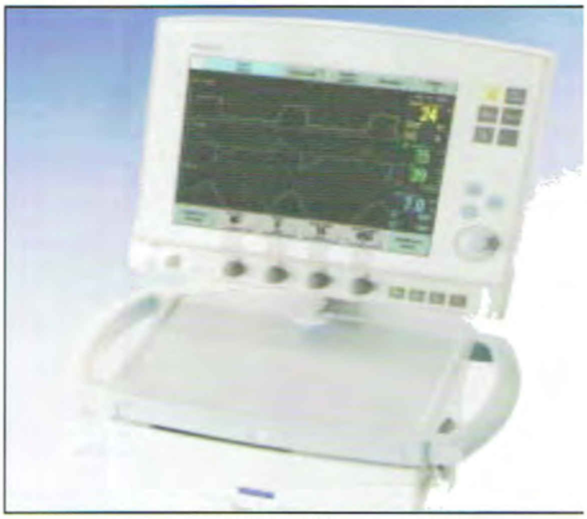


Fig. 35.15: Siemens servo

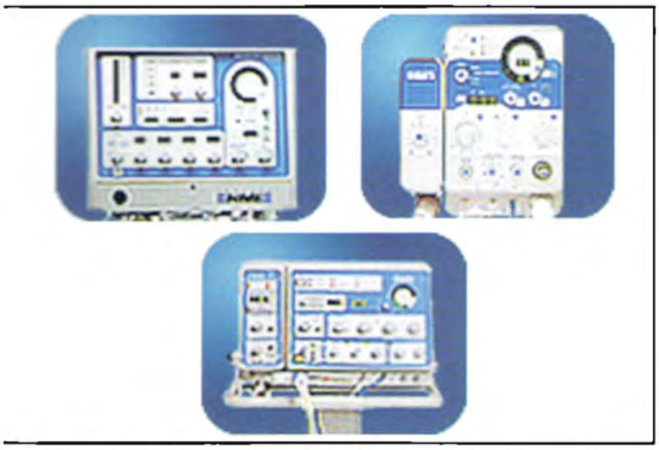


Fig. 35.12: Newport E100m, Newport Breeze E 150, Newport Wave E120, Newport E100M ventilator

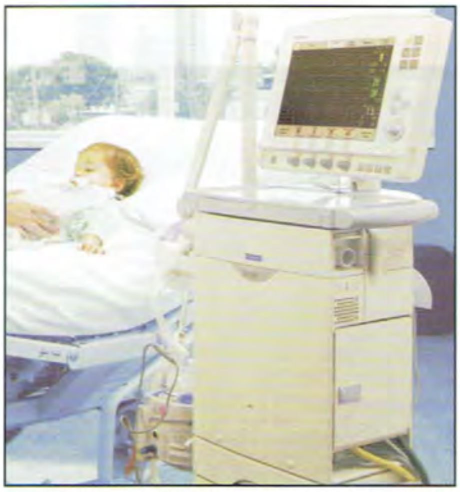


Fig. 35.16: Servo-i infant (Maquet)

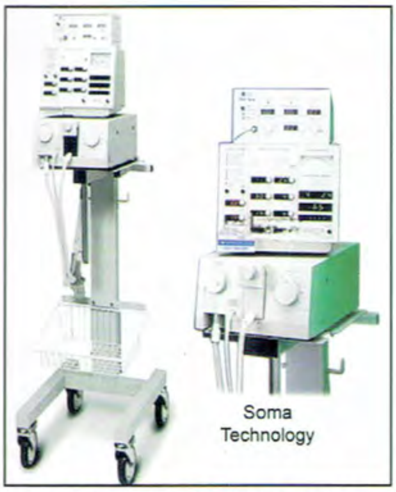


Fig. 35.14: Infant star 500/950 ventilator system

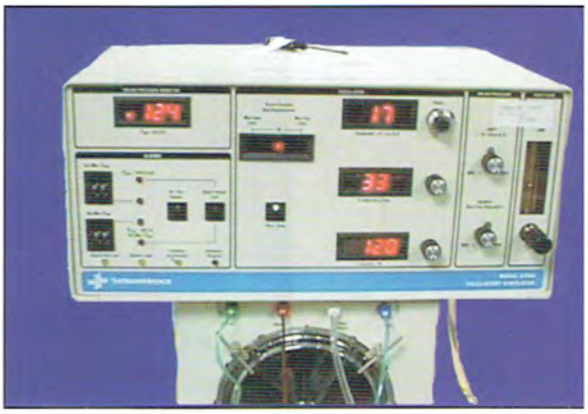


Fig. 35.17: Sensormedics 3100A

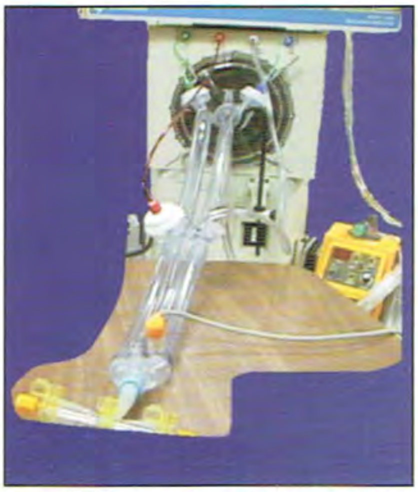


Fig. 35.18: Sensor medics high frequency oscillatory ventilators

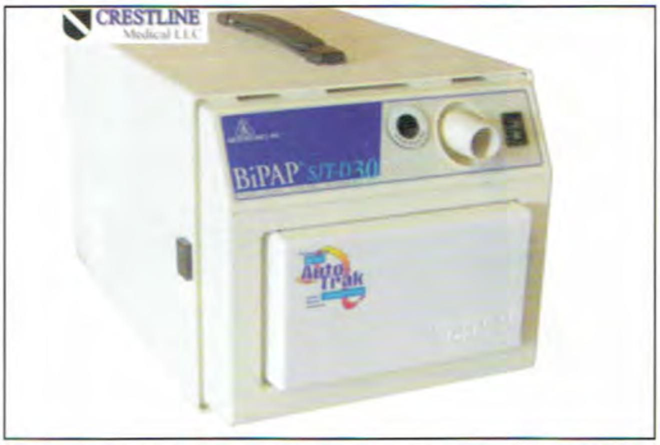
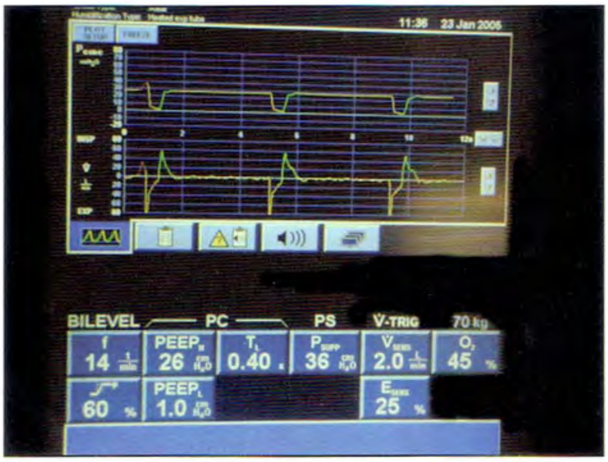

CRESTLINE
Medical LLC
BiPAP S/T-D30
Auto Trak

Fig. 35.19: Respironics BIPAP


11:36 23 Jan 2006

BILEVEL PC PS V-TRIG 70 kg
f 14
PEEP$_H$ 26
T$_L$ 0.40
P$_{SUPP}$ 36
V$_{SENS}$ 2.0
O$_2$ 45 %
60 %
PEEP$_L$ 1.0
E$_{SENS}$ 25 %

Fig. 36.1: APRV

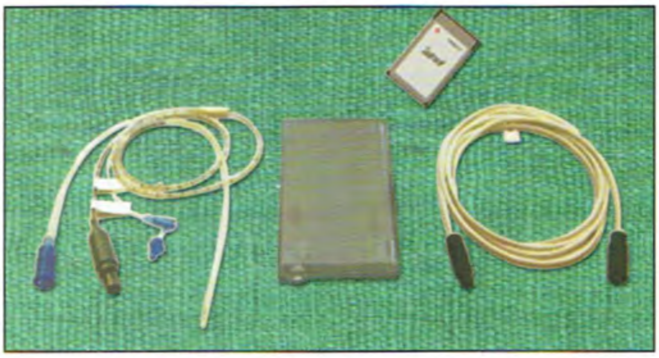


Fig. 36.6: Maquet

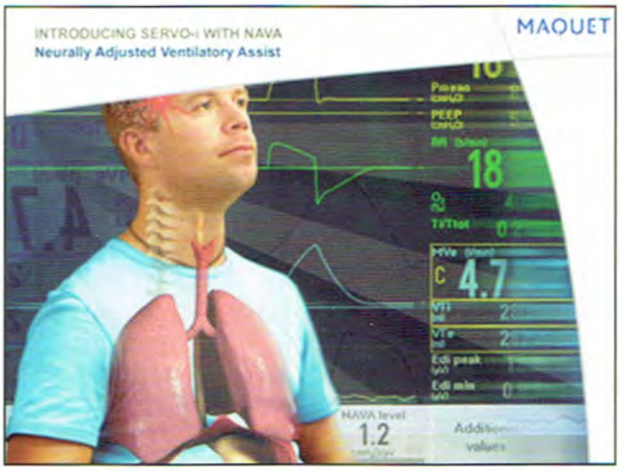
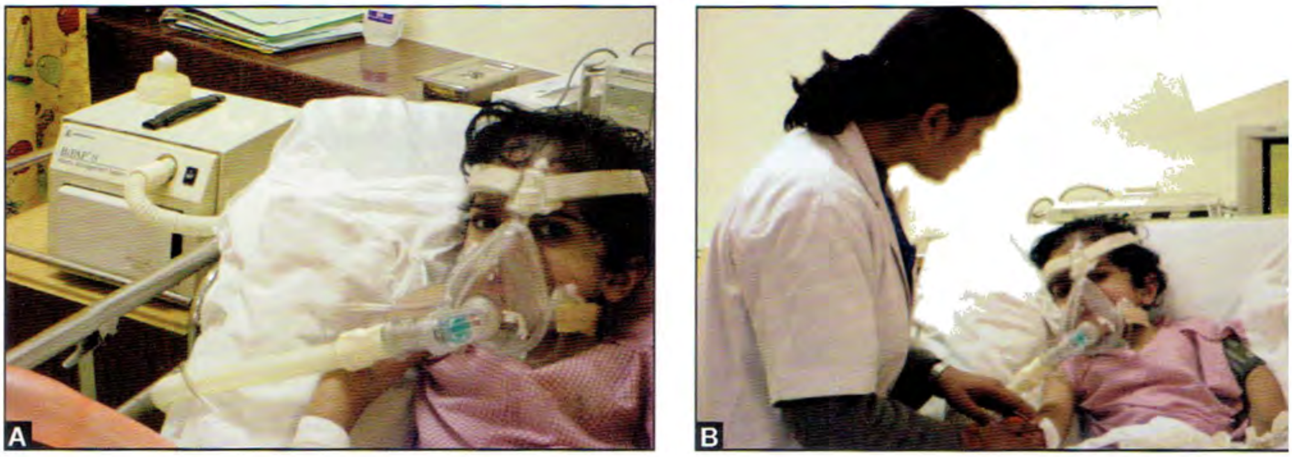

INTRODUCING SERVO-i WITH NAVA
Neurally Adjusted Ventilatory Assist
MAQUET
Pmean
PEEP
RR
18
O2
Ti/Ttot
MVe
4.7
VTi
VTe
Edi peak
Edi min
NAVA level
1.2
Additional values

Fig. 36.4: Naturally adjusted ventilatory assistance



Figs 41.1A and B: Patient on NIPPV (BIPAP on respironics NIPPV ventilator)

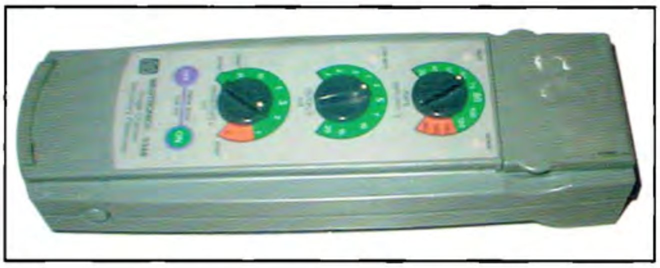


Fig. 59.1: Pacemaker

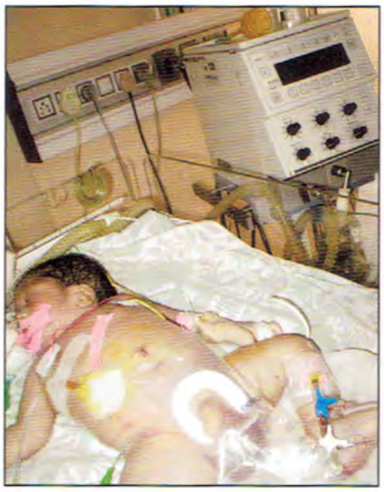


Fig. 65.2: Neonatal receiving peritoneal dialysis

Section One

Basic Practical Issues

CHAPTER 1 Managing Any Pediatric Emergency: A Practical Approach

Praveen Khilnani

In outpatient practice pediatric specialist as well as general practitioner comes across common pediatric illnesses frequently. It is important to recognize potentially life threatening conditions as well as conditions requiring immediate intervention and transfer to a higher level medical facility.

Besides accidental trauma, poisoning, insect bites, allergic reactions, common medical problems that bring the child to medical attention are fever, cough, respiratory distress, cyanosis, ear ache, poor feeding, vomiting, diarrhea, irritability, lethargy, convulsions and unresponsiveness.

Common conditions that require immediate attention are—respiratory distress, shock, lethargy and coma.

Since our main goal as a medical practitioner is to prevent unnecessary mortality and morbidity by prompt and early recognition of potential problems leading to respiratory or cardiorespiratory arrest, it is important to **pay attention** to following during history and physical examination DONE SIMULTANEOUSLY.

- Listen carefully to the mother.
- Do not ignore, it will not get better if something is not done.

Important general features signifying potentially serious problem include:

- Constantly crying child (unconsolable)
- Sick looking child refusing to feed
- Lethargic child
- Comatose child
- Child with respiratory distress (tachypnea, irregular respirations, nasal flaring, suprasternal, intercostal and subcostal retractions, grunting, head bobbing, stridor, wheezing, sweating, tired looking, gasping)
- Child in shock (is suggested by clinical findings of cool extremities, poor peripheral pulses, poor urination by history, lethargy, tachycardia, blood pressure normal or low).

CLINICAL ASSESSMENT

Perform rapid cardiopulmonary assessment.
Quick head to tow examination (TIME IS OF ESSENCE!) assessing:

Airway Noisy, nose block, congested, audible wheeze or stridor whether accessory muscles working.

Common conditions related to problems with upper airway include croup (laryngo tracheobronchitis), bacterial tracheitis, peritonsillar or retropharyngeal abscess, rarely epiglottitis.

Breathing Respiratory rate, tachypnea, grunting, accessory muscle use, nasal flaring, intercostal and subcostal retractions, cyanosis, crepitations, rales and wheezes. Common conditions causing respiratory distress include pneumonia and asthma, other conditions to be kept in mind include chest trauma causing a flail segment, hydropneumothorax, foreign body aspiration, near drowning, aspiration of gastric contents, pulmonary edema, pleural effusion, and empyema. SpO_2 should be checked by pulse oximetry.

Circulation Heart rate, pulse, blood pressure, capillary refill time.

Common conditions involving circulatory impairment include: hypovolemic shock, septic shock, cardiogenic shock, anaphylactic shock and neurogenic shock.

Central nervous system Lethargy, coma, GCS (Glas-gow Coma Scale), neck stiffness, convulsions.

Common conditions involving CNS include meningitis, encephalitis, metabolic encephalopathies and poisonings.

Note: Clinical assessment needs to be rapid and simultaneous with intervention for stabilization.

STABILIZATION

Things required at all practice locations (hospital or private practice): Oxygen, bag mask (ambu), intubating equipment, intraosseous needle, iv canula, iv fluids. Additionally: Suction, pulse oximeter and nebulizer.

- Once the critically ill child is recognized requiring intervention.
- Do not waste time in detailed investigations and diagnosis.
- Do the following regardless of diagnosis. Give oxygen.

If Respiratoy Distress

1. Ensure airway, i.e. open by head tilt, jaw thrust or chin lift maneuvers, if not open then intubate endotracheally and give bag ventilation. If can not intubate do bag and mask ventilation.
   If known foreign body obstruction then back blows, chest thrusts and Heimlich maneuver.
2. Nebulize as required (adrenaline or beta two stimulant) if pulse oximeter available, monitor oxygen saturation.

If Shock

1. Establish intravenous/intraosseous access. Do not waste more than 90 seconds on trying for intravenous access or wasting time with central line. Establish Intraosseous access.
2. PUSH fluid bolus—20 cc/kg isotonic fluid (normal saline or ringer lactate).
3. If known hypovolemia/suspected sepsis, or Dengue:3-4 fluid boluses 40 to 80 ml/kg fluid push may be required.

After Each Intervention Reassess

Airway, breathing and circulation (capillary refill, color, heart rate pulse blood pressure, mental status, urine output).

Other Supportive Therapy

1. Anticonvulsants—If convulsions diazepam iv/ rectal/midazolam iv (caution–respiratory depression respiratory arrest). Phenytoin/ Phenobarbitone intravenously.
2. Antipyretics/sponge if high fever.
3. Analgesics, if pain—Nonsteroidal anti-inflammatory agents narcotics as necessary.
4. Antiemetics, if vomiting.
5. Antiallergics—If allergic reaction/anaphylaxis (subcutaneous adrenaline antihistaminics, steroids).

After initial stabilization and ensuring airway breathing and circulation under reasonable control with established iv access, transfer/transport to a higher level facility needs to be arranged based on following indications for admission to pediatric intensive care unit.

Common Indications for the PICU Admission

1. All unstable patients.
2. Respiratory distress with or without mechanical ventilation (multiple causes).
3. All patients with shock (due to multiple causes with the exception of uncomplicated hypovolemia due to gastrointestinal losses).
4. All lethargic and comatose patients including:
   - Diabetic ketoacidosis
   - Hepatic failure
   - Concussion head injury
   - Major multi trauma
   - Convulsions
   - Poisonings.
5. Any patient with active bleeding.
6. Acute renal failure.
7. Near drowning.
8. All patients after successful resuscitation.
9. Postoperatively after complex major surgery.

SUMMARY

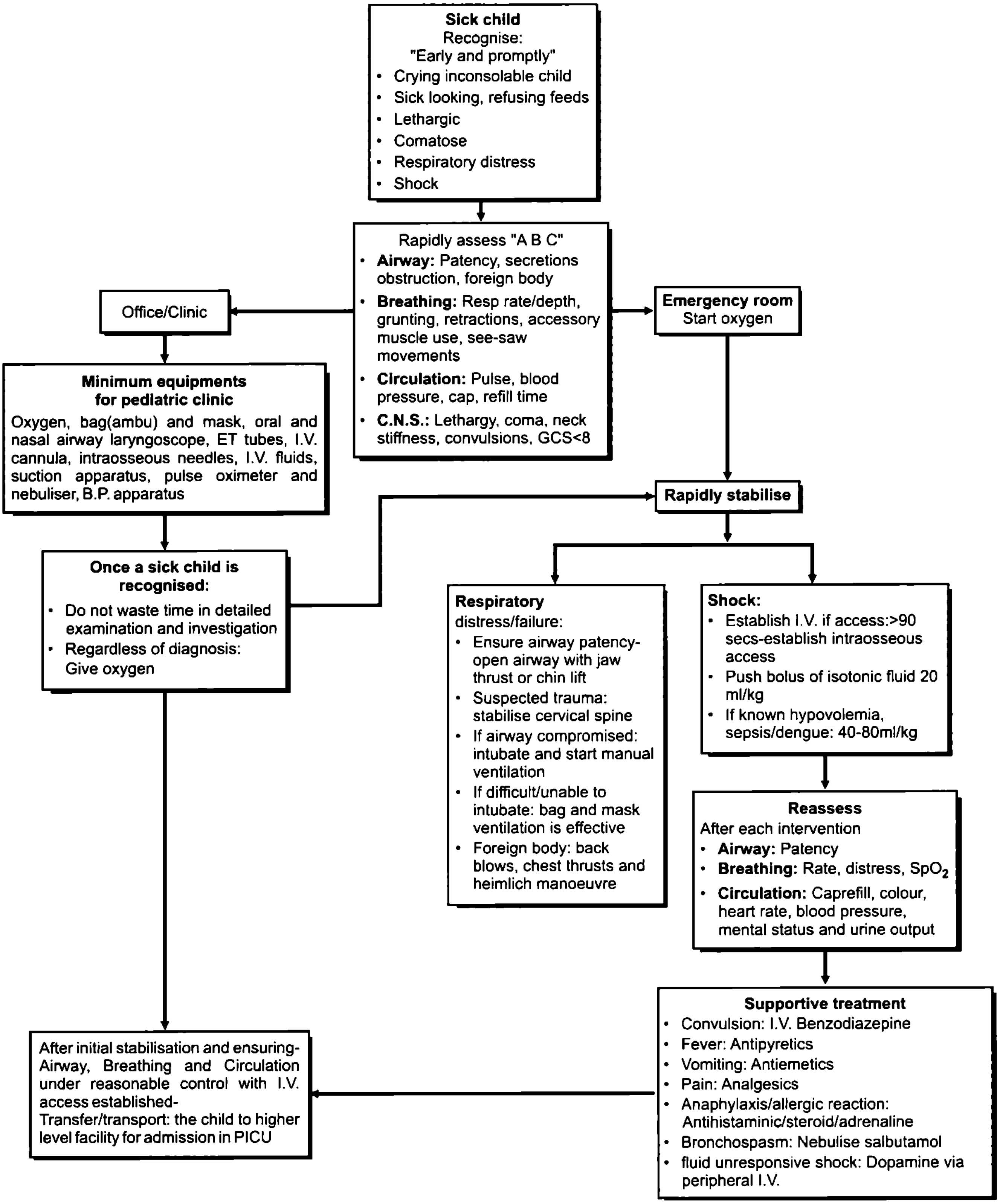
Stabilizing the Pediatric Patient (Flow chart 1.1)

1. *Goals in the care of the critically ill child:*
   a. Initial stabilization—Buys time until the child can get to the PICU.
   b. Safe and expedient transfer to a PICU.
   c. Definitive care—Fine tuning of diagnosis and therapy in the PICU.
2. *Operating principles of stabilization:*
   a. Focus the assessment and therapy on the crucial problems which are the life-and organ-threatening problems.
   b. The primary life-threatening problem in ALL emergencies is oxygen deficiency.
   c. Provide specific disease directed therapy.
3. *First goal of therapy* Rapidly restore and maintain oxygen delivery to the cells and tissues. A.airway B. Breathing C. Circulation.
4. *Oxygen delivery to the tissues:*
   a. Respiratory system—Need to consider both the PO_2 (partial pressure of oxygen) and SpO_2 (oxygen saturation).
   b. Cardiovascular system—Need to consider cardiac output.
   c. Hematologic system—Need to consider hemoglobin concentration and function.
5. *Brain injury* When significant brain injury exists, oxygen delivery to the brain may become dependent on the maintenance of an adequate cerebral perfusion pressure (Mean arterial pressure minus intracranial pressure).
6. *Four requirements of oxygen delivery:*
   a. SpO_2
   b. Cardiac output
   c. Hemoglobin concentration and function
   d. Cerebral perfusion pressure.
7. *Oxygen delivery* This is defined as the oxygen content in the blood times the cardiac output.
8. *Pathological states of decreased oxygen delivery:*
   a. Hypoxemia—Support increased cardiac output and increase hemoglobin levels.
   b. Severe anemia—Increase FiO_2 levels, support increased cardiac output and increase hemoglobin levels cautiously.
   c. Diminished cardiac output (shock)—Provide volume support before inotropes, increase FiO_2 and increase hemoglobin levels.
9. *Oxygen delivery and utilization:*
   a. Supply > need—ideal situation
   b. Supply < need—tissue hypoxia
      - Decrease the oxygen need by temperature control and measures that reduce body work such as mechanical ventilation, neuromuscular paralysis and sedation.
10. Typical cases
    a. Septic shock:
       - Volume—20 ml/kg IV push to start with and keep going until the patient starts to improve or the liver edge is palpable.
       - Inotropes—After volume expansion if not enough to compensate.
    b. Seizures—Be sure to check your ABC's before starting antiepileptic drugs.

TAKE HOME MESSAGE

- Solve immediate problem. Do not waste time in establishing precise diagnosis.
- Recognize critical illness, stabilize. Arrange transfer to a PICU. Ensure continued stabilization measure until care is handed over.

Flow chart 1.1: Managing the sick child



Sick child
Recognise:
"Early and promptly"

- Crying inconsolable child
- Sick looking, refusing feeds
- Lethargic
- Comatose
- Respiratory distress
- Shock

Rapidly assess "A B C"

- **Airway:** Patency, secretions obstruction, foreign body
- **Breathing:** Resp rate/depth, grunting, retractions, accessory muscle use, see-saw movements
- **Circulation:** Pulse, blood pressure, cap, refill time
- **C.N.S.:** Lethargy, coma, neck stiffness, convulsions, GCS<8

Office/Clinic

Minimum equipments for pediatric clinic
Oxygen, bag(ambu) and mask, oral and nasal airway laryngoscope, ET tubes, I.V. cannula, intraosseous needles, I.V. fluids, suction apparatus, pulse oximeter and nebuliser, B.P. apparatus

Once a sick child is recognised:

- Do not waste time in detailed examination and investigation
- Regardless of diagnosis: Give oxygen

Emergency room
Start oxygen

Rapidly stabilise

Respiratory distress/failure:

- Ensure airway patency-open airway with jaw thrust or chin lift
- Suspected trauma: stabilise cervical spine
- If airway compromised: intubate and start manual ventilation
- If difficult/unable to intubate: bag and mask ventilation is effective
- Foreign body: back blows, chest thrusts and heimlich manoeuvre

Shock:

- Establish I.V. if access:>90 secs-establish intraosseous access
- Push bolus of isotonic fluid 20 ml/kg
- If known hypovolemia, sepsis/dengue: 40-80ml/kg

Reassess
After each intervention

- **Airway:** Patency
- **Breathing:** Rate, distress, SpO_2
- **Circulation:** Caprefill, colour, heart rate, blood pressure, mental status and urine output

Supportive treatment

- Convulsion: I.V. Benzodiazepine
- Fever: Antipyretics
- Vomiting: Antiemetics
- Pain: Analgesics
- Anaphylaxis/allergic reaction: Antihistaminic/steroid/adrenaline
- Bronchospasm: Nebulise salbutamol
- fluid unresponsive shock: Dopamine via peripheral I.V.

After initial stabilisation and ensuring-Airway, Breathing and Circulation under reasonable control with I.V. access established-Transfer/transport: the child to higher level facility for admission in PICU

CHAPTER

2

Pediatric Basic Life Support

Praveen Khilnani, Anil Sachde

INTRODUCTION

For best survival and quality of life, pediatric basic life support (BLS) should be part of a community effort that includes prevention, basic CPR, prompt access to the emergency medical services (EMS) system, and prompt pediatric advanced life support (PALS). These 4 links form the American Heart Association (AHA) Pediatric Chain of Survival (Fig. 2.1). The first 3 links constitute pediatric BLS.

Rapid and effective bystander CPR is associated with successful return of spontaneous circulation and neurologically intact survival in children. The greatest impact occurs in respiratory arrest, in which neurologically intact survival rates of >70% are possible, and in ventricular fibrillation (VF), in which survival rates of 30% have been documented. But only 2% to 10% of all children who develop out-of-hospital cardiac arrest survive, and most are neurologically devastated. Part of the disparity is that bystander CPR is provided for less than half of the victims of out-of-hospital arrest. Some studies show that survival and neurologic outcome can be improved with prompt CPR.

The BLS Sequence for Infants and Children

For the purposes of these guidelines, an "infant" is less than approximately 1 year of age. This section does not deal with newborn infants (see Chapter 3). For lay rescuers the "child" BLS guidelines should be applied when performing CPR for a child from about 1 year of age to about 8 years of age. For a health care provider, the pediatric ("child") guidelines apply from about 1 year to about the start of puberty. These guidelines delineate a series of skills as a sequence of distinct steps, but they are often performed simultaneously (eg, starting CPR and activating the EMS system), especially when more than one rescuer is present. This sequence is depicted in the Pediatric Health care Provider BLS Algorithm (Fig. 2.2). The numbers listed with the headings below refer to the corresponding box in that algorithm.

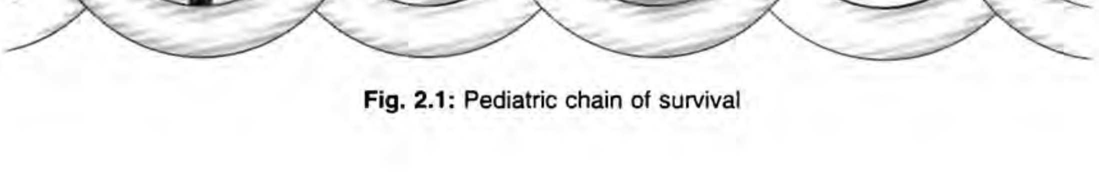
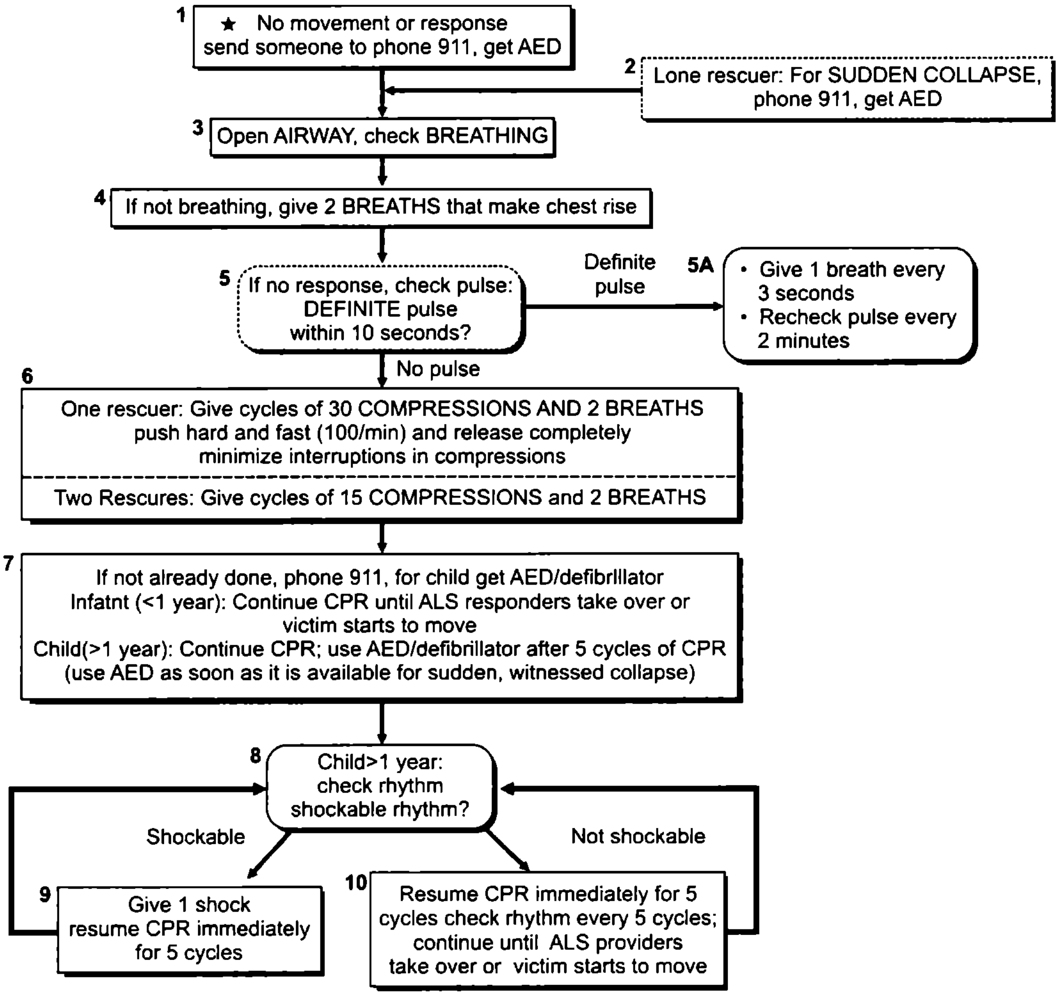


Fig. 2.1: Pediatric chain of survival


1
★ No movement or response
send someone to phone 911, get AED
2
Lone rescuer: For SUDDEN COLLAPSE,
phone 911, get AED
3
Open AIRWAY, check BREATHING
4
If not breathing, give 2 BREATHS that make chest rise
5
If no response, check pulse:
DEFINITE pulse
within 10 seconds?
Definite
pulse
5A
• Give 1 breath every
3 seconds
• Recheck pulse every
2 minutes
No pulse
6
One rescuer: Give cycles of 30 COMPRESSIONS AND 2 BREATHS
push hard and fast (100/min) and release completely
minimize interruptions in compressions
Two Rescures: Give cycles of 15 COMPRESSIONS and 2 BREATHS
7
If not already done, phone 911, for child get AED/defibrlllator
Infatnt (<1 year): Continue CPR until ALS responders take over or
victim starts to move
Child(>1 year): Continue CPR; use AED/defibrillator after 5 cycles of CPR
(use AED as soon as it is available for sudden, witnessed collapse)
8
Child>1 year:
check rhythm
shockable rhythm?
Shockable
Not shockable
9
Give 1 shock
resume CPR immediately
for 5 cycles
10
Resume CPR immediately for 5
cycles check rhythm every 5 cycles;
continue until ALS providers
take over or victim starts to move

★ 911 – not applicable in India use emergency number (local)
AED – Automatic External defibrillator is ideal but not universally available

Fig. 2.2: BLS algorithm

Safety of Rescuer and Victim

Always make sure that the area is safe for you and the victim. Move a victim only to ensure the victim's safety. Although exposure to a victim while providing CPR carries a theoretical risk of infectious disease transmission, the risk is very low.

Check for Response (Box 1)

Gently tap the victim and ask loudly, "Are you okay?" Call the child's name if you know it.

Look for movement. If the child is responsive, he or she will answer or move. Quickly check to see if the child has any injuries or needs medical assistance. If necessary, leave the child to phone the emergency ambulance, but return quickly and recheck the child's condition frequently. Children with respiratory distress often assume a position that maintains airway patency and optimizes ventilation. Allow the child with respiratory distress to remain in a position that is most comfortable.

If the child is unresponsive and is not moving, shout for help and start CPR. If you are alone, continue CPR for 5 cycles (about 2 minutes). One cycle of CPR for the lone rescuer is 30 compressions and 2 breaths. If a second rescuer is present, that rescuer should immediately call for emergency ambulance and get an AED (if the child is 1 year of age or older) while you continue CPR. If you suspect trauma, the second rescuer may assist by stabilizing the child's cervical spine. If the child must be moved for safety reasons, support the head and body to minimize turning, bending, or twisting of the head and neck.

Activate the EMS System and Get the AED (Box 2)

(Not ususally applicable in Indian scenario).

For simplicity of lay rescuer education it is acceptable for the lone lay rescuer to provide about 5 cycles (about 2 minutes) of CPR for any infant or child victim before leaving to phone for emergency ambulance and get an AED (if applicable). This sequence may be tailored for some learners (eg, the mother of a child at high risk for a sudden arrhythmia). If two rescuers are present, one rescuer should begin CPR while the other rescuer calls for the ambulance with AED.

Position the Victim

If the victim is unresponsive, make sure that the victim is in a supine (face up) position on a flat, hard surface, such as a sturdy table, the floor, or the ground. If you must turn the victim, minimize turning or twisting of the head and neck.

Open the Airway and Check Breathing (Box 3)

In an unresponsive infant or child, the tongue may obstruct the airway, so the rescuer should open the airway.

Open the Airway: Lay Rescuer

If you are a lay rescuer, open the airway using a head tilt–chin lift maneuver for both injured and noninjured victims (Fig. 2.3). The jaw thrust is no longer recommended for lay rescuers because it is difficult to learn and perform, is often not an effective way to open the airway, and may cause spinal movement.

Open the Airway: Health Care Provider

A health care provider should use the head tilt–chin lift maneuver to open the airway of a victim without evidence of head or neck trauma.

Approximately 2% of all victims with blunt trauma requiring spinal imaging in an emergency department have a spinal injury. This risk is tripled if the victim has craniofacial injury, a Glasgow Coma Scale score of <8, or both. If you are a health care provider and suspect that the victim may have a cervical spine injury, open the airway using a jaw thrust withou head tilt (Fig. 2.4). Because maintaining a paten airway and providing adequate ventilation is a priority in CPR, use a head tilt–chin lift maneuver i the jaw thrust does not open the airway.

Check Breathing (Box 3)

While maintaining an open airway, take no more than 10 seconds to check whether the victim is breathing: Look for rhythmic chest and abdomina movement, listen for exhaled breath sounds at the nose and mouth, and feel for exhaled air on your cheek. Periodic gasping, also called agonal gasps, is not breathing.

If the child is breathing and there is no evidence of trauma: turn the child onto the side (recovery position, Figure 2.5). This helps maintain a paten airway and decreases risk of aspiration.

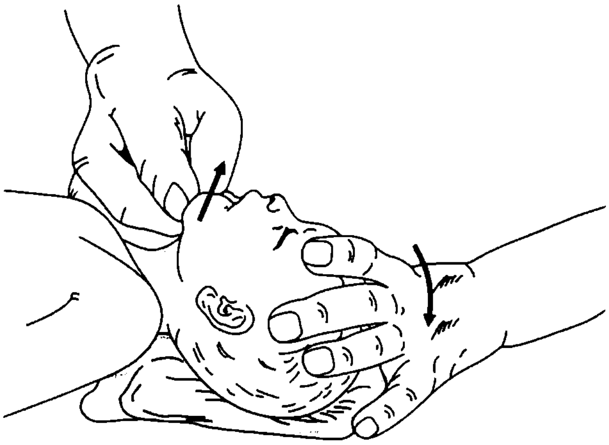


Fig. 2.3: Head tilt chin lift

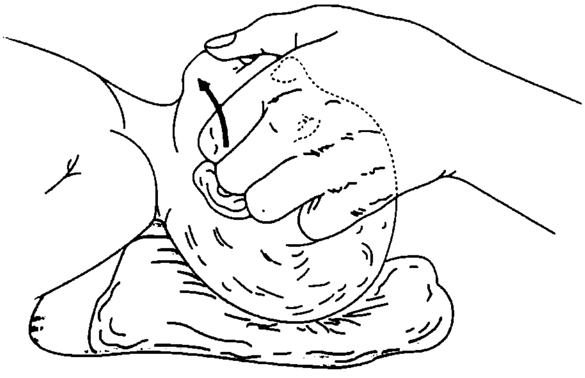


Fig. 2.4: Jaw thrust

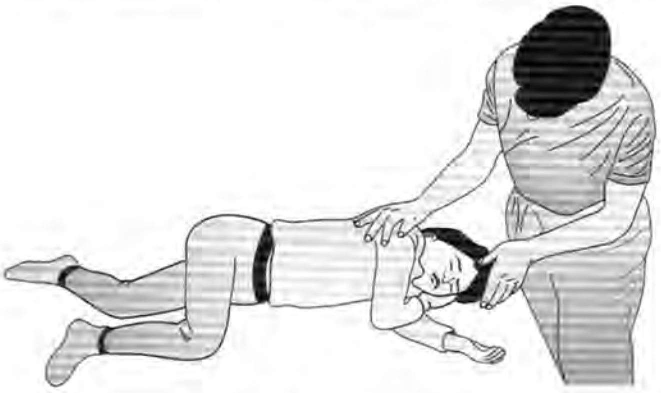


Fig. 2.5: Recovery position

Give Rescue Breaths (Box 4)

If the child is not breathing or has only occasional gasps:

- For the lay rescuer: maintain an open airway and give 2 breaths.
- For the health care provider: maintain an open airway and give 2 breaths. Make sure that the breaths are effective (i.e., the chest rises). If the chest does not rise, reposition the head, make a better seal, and try again. It may be necessary to move the child's head through a range of positions to obtain optimal airway patency and effective rescue breathing.

In an infant, use a mouth-to-mouth-and-nose technique; in a child, use a mouth-to-mouth technique (Figs 2.6 and 2.7).

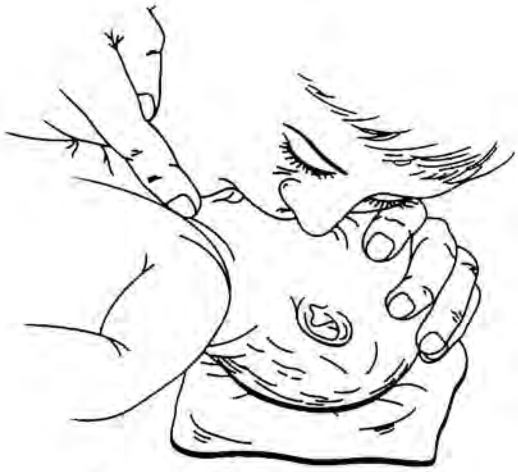


Fig. 2.6: Rescue breath-infant

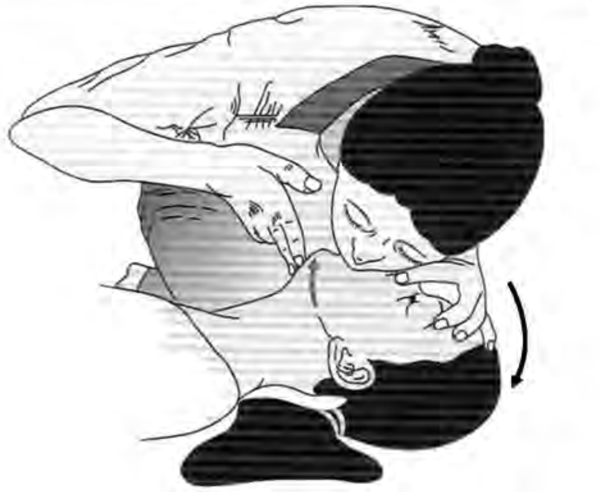


Fig. 2.7: Rescue breath-child

Comments on Technique

In an infant, if you have difficulty making an effective seal over the mouth and nose, try either mouth-to-mouth or mouth-to-nose ventilation. If you use the mouth-to-mouth technique, pinch the nose closed. If you use the mouth-to-nose technique, close the mouth. In either case make sure the chest rises when you give a breath.

Barrier Devices

Despite its safety, some health care providers and lay rescuers may hesitate to give mouth-to-mouth rescue breathing and prefer to use a barrier device. Barrier devices have not reduced the risk of transmission of infection, and some may increase resistance to air flow. If you use a barrier device, do not delay rescue breathing.

Bag-Mask Ventilation (Health Care Providers)

Bag-mask ventilation can be as effective as endotracheal intubation and safer when providing ventilation for short periods. But bag-mask ventilation requires training and periodic retraining in the following skills: selecting the correct mask size, opening the airway, making a tight seal between the mask and face, delivering effective ventilation, and assessing the effectiveness of that ventilation. In the out-of-hospital setting, preferentially ventilate and oxygenate infants and children with a bag and mask rather than attempt intubation if transport time is short.

Ventilation Bags

Use a self-inflating bag with a volume of at least 450 to 500 mL; smaller bags may not deliver an effective tidal volume or the longer inspiratory times required by full-term neonates and infants.

A self-inflating bag delivers only room air unless supplementary oxygen is attached, but even with an oxygen inflow of 10 L/min, the concentration of delivered oxygen varies from 30% to 80% and depends on the tidal volume and peak inspiratory flow rate. To deliver a high oxygen concentration (60% to 95%), attach an oxygen reservoir to the self-inflating bag. You must maintain an oxygen flow of 10 to 15 L/min into a reservoir attached to a pediatric bag and a flow of at least 15 L/min into an adult bag.

Precautions

Avoid hyperventilation; use only the force and tidal volume necessary to make the chest rise. Give each breath over 1 second.

- In a victim of cardiac arrest with no advanced airway in place, pause after 30 compressions (1 rescuer) or 15 compressions (2 rescuers) to give 2 ventilations when using either mouth-to-mouth or bag-mask technique.
- During CPR for a victim with an advanced airway (eg, endotracheal tube, esophageal-tracheal combitube, or laryngeal mask airway [LMA]) in place, rescuers should no longer deliver "cycles" of CPR. The compressing rescuer should compress the chest at a rate of 100 times per minute without pauses for ventilations, and the rescuer providing the ventilation should deliver 8 to 10 breaths per minute. Two or more rescuers should change the compressor role approximately every 2 minutes to prevent compressor fatigue and deterioration in quality and rate of chest compressions.
- If the victim has a perfusing rhythm (ie, pulses are present) but no breathing, give 12 to 20 breaths per minute (1 breath every 3 to 5 seconds).

Health care providers often deliver excessive ventilation during CPR, particularly when an advanced airway is in place. Excessive ventilation is detrimental because it:

- Impedes venous return and therefore decreases cardiac output, cerebral blood flow, and coronary perfusion by increasing intrathoracic pressure.
- Causes air trapping and barotrauma in patients with small-airway obstruction.
- Increases the risk of regurgitation and aspiration.

Rescuers should provide the recommended number of rescue breaths per minute.

You may need high pressures to ventilate patients with airway obstruction or poor lung compliance. A pressure-relief valve can prevent delivery of sufficient tidal volume. Make sure that the manual bag allows you to use high pressures if necessary to achieve visible chest expansion.

Two-Person Bag-Mask Ventilation

A 2-person technique may be necessary to provide effective bag-mask ventilation when there is significant airway obstruction, poor lung compliance, or difficulty in creating a tight seal between the mask and the face. One rescuer uses both hands to open the airway and maintain a tight mask-to-face seal while the other compresses the ventilation bag. Both rescuers should observe the chest to ensure chest rise.

Gastric Inflation and Cricoid Pressure

Gastric inflation may interfere with effective ventilation and cause regurgitation. To minimize gastric inflation:

- Avoid excessive peak inspiratory pressures (e.g., ventilate slowly).
- Apply cricoid pressure. Do this only in an unresponsive victim and if there is a second rescuer. Avoid excessive pressure so as not to obstruct the trachea.

Oxygen

Despite animal and theoretic data suggesting possible adverse effects of 100% oxygen, there are no studies comparing various concentrations of oxygen during resuscitation beyond the newborn period. Until additional information becomes available, health care providers should use 100% oxygen during resuscitation. Once the patient is stable, wean supplementary oxygen but ensure adequate oxygen delivery by appropriate monitoring. Whenever possible, humidify oxygen to prevent mucosal drying and thickening of pulmonary secretions.

Masks

Masks provide an oxygen concentration of 30% to 50% to a victim with spontaneous breathing. For a higher concentration of oxygen, use a tight-fitting nonrebreathing mask with an oxygen inflow rate of approximately 15 L/min that maintains inflation of the reservoir bag.

Nasal Cannulas

Infant and pediatric size nasal cannulas are suitable for children with spontaneous breathing. The concentration of delivered oxygen depends on the child's size, respiratory rate, and respiratory effort. For example, a flow rate of only 2 L/min can provide young infants with an inspired oxygen concentration >50%.

Pulse Check (for Health Care Providers) (Box 5)

If you are a health care provider, you should try to palpate a pulse (brachial in an infant and carotid or femoral in a child). Take no more than 10 seconds. Studies show that health care providers as well as lay rescuers are unable to reliably detect a pulse and at times will think a pulse is present when there is no pulse. For this reason, if you do not definitely feel a pulse (e.g., there is no pulse or you are not sure you feel a pulse) within 10 seconds, proceed with chest compressions.

If despite oxygenation and ventilation the pulse is <60 beats per minute (bpm) and there are signs of poor perfusion (ie, pallor, cyanosis), begin chest compressions. Profound bradycardia in the presence of poor perfusion is an indication for chest compressions because an inadequate heart rate with poor perfusion indicates that cardiac arrest is imminent. Cardiac output in infancy and childhood largely depends on heart rate. No scientific data has identified an absolute heart rate at which chest compressions should be initiated; the recommendation to provide cardiac compression for a heart rate <60 bpm with signs of poor perfusion is based on ease of teaching and skills retention. For additional information see algorhithm "Bradycardia" in chapter on: "Pediatric Advanced Life Support."

If the pulse is 60 bpm but the infant or child is not breathing, provide rescue breathing without chest compressions.

Lay rescuers are not taught to check for a pulse. The lay rescuer should immediately begin chest compressions after delivering 2 rescue breaths.

Rescue Breathing Without Chest Compressions (for Health Care Providers Only) (Box 5A)

If the pulse is 60 bpm but there is no spontaneous breathing or inadequate breathing, give rescue breaths at a rate of about 12 to 20 breaths per minute (1 breath every 3 to 5 seconds) until spontaneous breathing resumes (Box 5A). Give each breath over 1 second. Each breath should cause visible chest rise.

During delivery of rescue breaths, reassess the pulse about every 2 minutes, but spend no more than 10 seconds doing so.

Chest Compressions (Box 6)

To give chest compressions, compress the lower half of the sternum but do not compress over the xiphoid. After each compression allow the chest to recoil fully because complete chest reexpansion improves blood flow into the heart. A manikin study showed that one way to ensure complete recoil is to lift your hand slightly off the chest at the end of each compression, but this has not been studied in humans (Class Indeterminate). The following are characteristics of good compressions:

- "Push hard": push with sufficient force to depress the chest approximately one third to one half the anterior-posterior diameter of the chest.
- "Push fast": push at a rate of approximately 100 compressions per minute.
- Release completely to allow the chest to fully recoil.
- Minimize interruptions in chest compressions.

In an infant victim, lay rescuers and lone rescuers should compress the sternum with 2 fingers (Fig. 2.8) placed just below the intermammary line.

The 2 thumb–encircling hands technique (Fig. 2.9) is recommended for health care providers when 2 rescuers are present. Encircle the infant's chest with both hands; spread your fingers around the thorax, and place your thumbs together over the lower half of the sternum. Forcefully compress the sternum with your thumbs as you squeeze the thorax with your fingers for counterpressure. If you are alone or you cannot physically encircle the victim's chest,

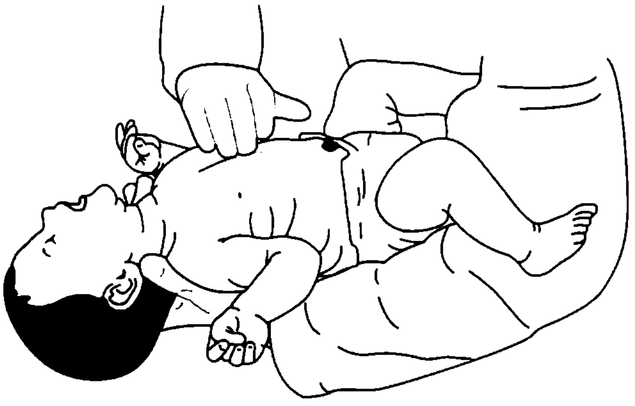


Fig. 2.8: Chest compressions

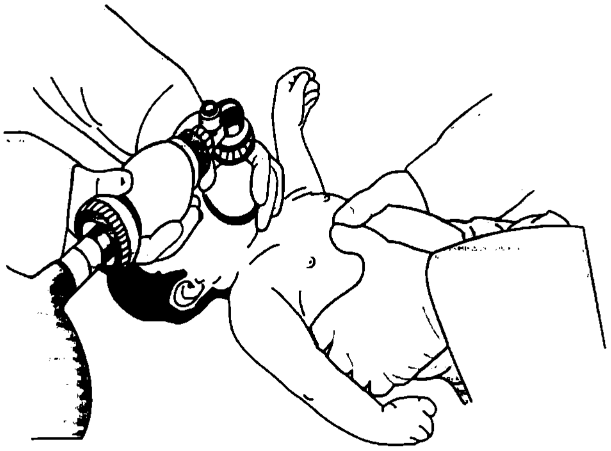


Fig. 2.9: The 2 thumb-encircling hands technique of CPR

compress the chest with 2 fingers. The 2 thumb–encircling hands technique is preferred because it produces higher coronary artery perfusion pressure, more consistently results in appropriate depth or force of compression, and may generate higher systolic and diastolic pressures.

In a child, lay rescuers and health care providers should compress the lower half of the sternum with the heel of 1 hand or with 2 hands (as used for adult victims) but should not press on the xiphoid or the ribs. There is no outcome data that shows a 1-hand or 2-hand method to be superior; higher compression pressures can be obtained on a child manikin with 2 hands. Because children and rescuers come in all sizes, rescuers may use either 1 or 2 hands to compress the child's chest. It is most important that the chest be compressed about one third to one half the anterior-posterior depth of the chest.

Coordinate Chest Compressions and Breathing (Box 6)

The ideal compression-ventilation ratio is unknown, but studies have emphasized the following:

- In 2000 a compression-ventilation ratio of 5:1 and a compression rate of 100 per minute were recommended. But at that ratio and compression rate, fewer than 50 compressions per minute were performed in an adult manikin, and fewer than 60 compressions per minute were performed in a pediatric manikin even under ideal circumstances.
- It takes a number of chest compressions to raise coronary perfusion pressure, which drops with each pause (eg, to provide rescue breathing, check for a pulse, attach an AED).
- Long and frequent interruptions in chest compressions have been documented during CPR by lay rescuers and by health care providers in the out-of-hospital and in-hospital settings. Interruptions in chest compressions are associated with decreased rate of return of spontaneous circulation.
- Ventilations are relatively less important during the first minutes of CPR for victims of a sudden arrhythmia-induced cardiac arrest [ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT)] than they are after asphyxia-induced arrest, but even in asphyxial arrest, a minute ventilation that is lower than normal is likely to maintain an adequate ventilation-perfusion ratio because cardiac output and, therefore, pulmonary blood flow produced by chest compressions is quite low.
- For lay rescuers, a single compression-ventilation ratio (30:2) for all age groups may increase the number of bystanders who perform CPR because it is easier to remember.

If you are the only rescuer, perform cycles of 30 chest compressions followed by 2 effective ventilations with as short a pause in chest compressions as possible. Make sure to open the airway before giving ventilations.

For 2-rescuer CPR (e.g., by health care providers or others, such as lifeguards, who are trained in this technique), one provider should perform chest compressions while the other maintains the airway and performs ventilations at a ratio of 15:2 with as short a pause in compressions as possible. Do not ventilate and compress the chest simultaneously with either mouth-to-mouth or bag-mask ventilation. The 15:2 ratio for 2 rescuers is applicable in children up to the start of puberty.

Rescuer fatigue can lead to inadequate compression rate and depth and may cause the rescuer to fail to allow complete chest wall recoil between compressions. The quality of chest compressions deteriorates within minutes even when the rescuer denies feeling fatigued. Once an advanced airway is in place for infant, child, or adult victims, 2 rescuers no longer deliver cycles of compressions interrupted with pauses for ventilation. Instead, the compressing rescuer should deliver 100 compressions per minute continuously without pauses for ventilation. The rescuer delivering the ventilations should give 8 to 10 breaths per minute and should be careful to avoid delivering an excessive number of ventilations. Two or more rescuers should rotate the compressor role approximately every 2 minutes to prevent compressor fatigue and deterioration in quality and rate of chest compressions. The switch should be accomplished as quickly as possible (ideally in less than 5 seconds) to minimize interruptions in chest compressions.

Compression-Only CPR

Ventilation may not be essential in the first minutes of VF cardiac arrest, during which periodic gasps and passive chest recoil may provide some ventilation if the airway is open. This, however, is not true for most cardiac arrests in infants and children, which are more likely to be asphyxial cardiac arrest. These victims require both prompt ventilations and chest compressions for optimal resuscitation. If a rescuer is unwilling or unable to provide ventilations, chest compressions alone are better than no resuscitation at all.

Activate the EMS System and Get the AED (Box 7) (may not be applicable in the Indian scenario)

In the majority of infants and children with cardiac arrest, the arrest is asphyxial. Lone rescuers (with the exception of health care providers who witness sudden collapse) should perform CPR for 5 cycles (about 2 minutes) before calling the ambulance, then start CPR again with as few interruptions of chest compressions as possible. If there are more rescuers present, one rescuer should begin the steps of CPR as soon as the infant or child is found to be unresponsive and a second rescuer should call the ambulance. Minimize interruption of chest compressions.

Defibrillation (Box 8)

VF can be the cause of sudden collapse, or it may develop during resuscitation attempts.[7,134] Children with sudden witnessed collapse (eg, a child collapsing during an athletic event) are likely to have VF or pulseless VT and need immediate CPR and rapid defibrillation. VF and pulseless VT are referred to as "shockable rhythms" because they respond to electric shocks (defibrillation) (Fig. 2.10).

Many AEDs have high specificity in recognizing pediatric shockable rhythms, and some are equipped to decrease the delivered energy to make it suitable for children 1 to 8 years of age. Since the publication of the ECC Guidelines 2000, data has shown that AEDs can be safely and effectively used in children 1 to 8 years of age. However, there is insufficient data to make a recommendation for or against using an AED in infants <1 year of age (Class Indeterminate).

In systems and institutions that care for children and have an AED program, it is recommended that

Fig. 2.10: Defibrillator

the AED have both a high specificity in recognizing pediatric shockable rhythms and a pediatric dose-attenuating system to reduce the dose delivered by the device. In an emergency if an AED with a pediatric attenuating system is not available, use a standard AED. Turn the AED on, follow the AED prompts, and resume chest compressions immediately after the shock. Minimize interruptions in chest compressions.

CPR Techniques and Adjuncts

There is insufficient data in infants and children to recommend for or against the use of mechanical devices to compress the sternum, active compression-decompression CPR, interposed abdominal compression CPR (IAC-CPR), or the impedance threshold device.

Foreign-Body Airway Obstruction (Choking)

Epidemiology and Recognition

More than 90% of deaths from foreign-body aspiration occur in children <5 years of age; 65% of the victims are infants. Liquids are the most common cause of choking in infants, whereas balloons, small objects, and foods (e.g. hot dogs, round candies, nuts, and grapes) are the most common causes of foreign-body airway obstruction (FBAO) in children. Signs of FBAO include a sudden onset of respiratory distress with coughing, gagging, stridor (a high-pitched, noisy sound), or wheezing. The characteristics that distinguish FBAO from other causes (e.g. croup) are sudden onset in a proper setting and the absence of antecedent fever or respiratory symptoms.

Relief of FBAO

FBAO may cause mild or severe airway obstruction. When the airway obstruction is mild, the child can cough and make some sounds. When the airway obstruction is severe, the victim cannot cough or make any sound.

- If FBAO is mild, do not interfere. Allow the victim to clear the airway by coughing while you observe for signs of severe FBAO.
- If the FBAO is severe (ie, the victim is unable to make a sound):

— For a child, perform subdiaphragmatic abdominal thrusts (Heimlich maneuver) Figs 2.11 and 2.12 until the object is expelled or the victim becomes unresponsive.

For an infant, deliver 5 back blows (slaps) (Fig. 2.13) followed by 5 chest thrusts repeatedly (Fig. 2.14) until the object is expelled or the victim becomes unresponsive. Abdominal thrusts are not recommended for infants because they may damage the relatively large and unprotected liver.

- If the victim becomes unresponsive, lay rescuers and health care providers should perform CPR but should look into the mouth before giving breaths. If you see a foreign body, remove it. Health care providers should not perform blind finger sweeps because they may push obstructing objects further into the pharynx and may damage the oropharynx. Health care providers should attempt to remove an object only if they can see it in the pharynx. Then rescuers should attempt ventilation and follow with chest compressions.

SPECIAL RESUSCITATION SITUATIONS

Children With Special Health Care Needs

Children with special health care needs may require emergency care for complications of chronic conditions (eg, obstruction of a tracheostomy), failure of support technology (eg, ventilator failure), progression of underlying disease, or events unrelated to those special needs. Care is often complicated by a lack of medical information, plan of medical care, list of current medications. Parents and child-care providers are encouraged to keep copies of medical information at home, with the child, and at the child's school or child-care facility.

When a child with a chronic or potentially life-threatening condition is discharged from the hospital, parents, school nurses, and home health care providers should be informed about the reason for hospitalization, hospital course, and how to recognize signs of deterioration. They should receive specific instructions about CPR and whom to contact.

Ventilation with a Tracheostomy or Stoma

Everyone involved with the care of a child with a tracheostomy (parents, school nurses, and home health care providers) should know how to assess patency of the airway, clear the airway, and perform CPR using the artificial airway.

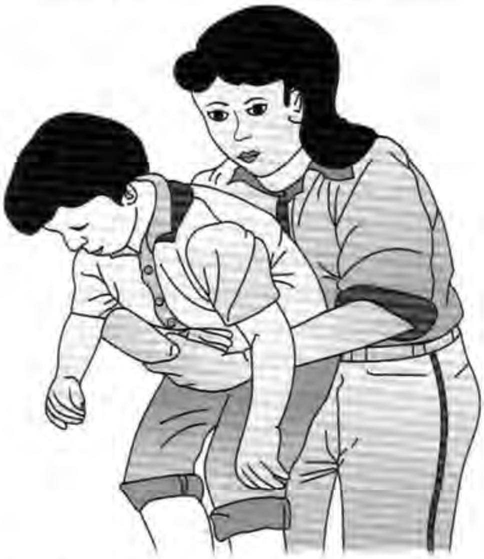


Fig. 2.11: Heimlich maneuver-conscious child

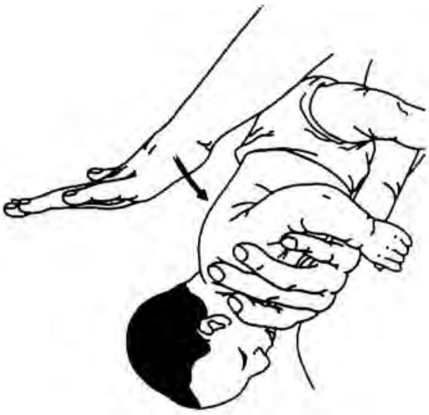


Fig. 2.13: Back blows

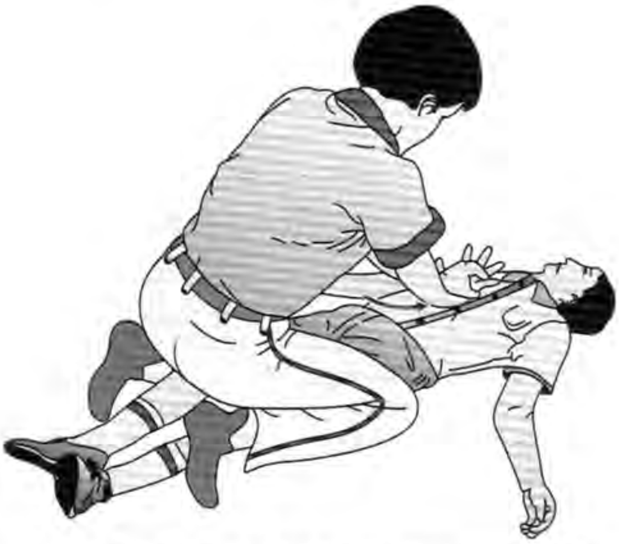


Fig. 2.12: Heimlich maneuver-unconscious child

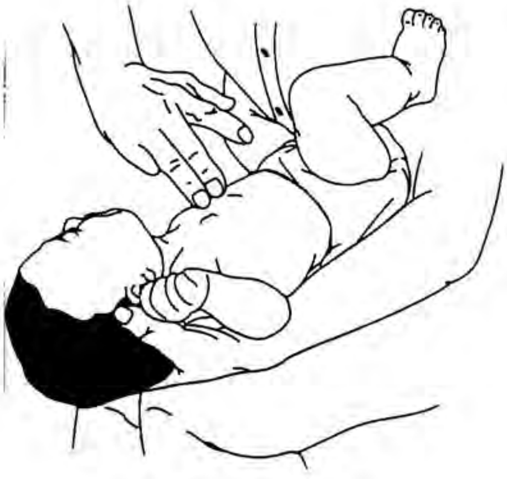


Fig. 2.14: Chest thrusts

Use the tracheostomy tube for ventilation and verify adequacy of airway and ventilation by watching for chest expansion. If the tracheostomy tube does not allow effective ventilation even after suctioning, replace it. Alternative ventilation methods include mouth-to-stoma ventilation and bag-mask ventilation through the nose and mouth while you or someone else occludes the tracheal stoma.

Trauma

The principles of BLS resuscitation for the injured child are the same as those for the ill child, but some aspects require emphasis; improper resuscitation is a major cause of preventable pediatric trauma death. Errors include failure to properly open and maintain the airway and failure to recognize and treat internal bleeding.

The following are important aspects of resuscitation of pediatric victims of trauma:

- Anticipate airway obstruction by dental fragments, blood, or other debris. Use a suction device if necessary.
- Stop all external bleeding with pressure.
- When the mechanism of injury is compatible with spinal injury, minimize motion of the cervical spine and avoid traction or movement of the head and neck. Open and maintain the airway with a jaw thrust and try not to tilt the head. If a jaw thrust does not open the airway, use a head tilt–chin lift. If there are 2 rescuers, the first opens the airway while the second restricts cervical spine motion. To limit spine motion, secure at least the thighs, pelvis, and shoulders to the immobilization board. Because of the disproportionately large size of the head in infants and young children, optimal positioning may require recessing the occiput or elevating the torso to avoid undesirable backboard-induced cervical flexion.
- If possible, transport children with multisystem trauma to a tertiary level center with pediatric expertise.

Drowning

Outcome after drowning depends on the duration of submersion, the water temperature, and how promptly CPR is started. An excellent outcome can occur after prolonged submersion in icy waters. Star resuscitation by safely removing the victim from the water as rapidly as possible. If you have special training, start rescue breathing while the victim is still in the water if doing so will not delay removing the victim from the water. Do not attempt chest compressions in the water, however.

There is no evidence that water acts as an obstructive foreign body; don't waste time trying to remove water from the victim. Start CPR by opening the airway and giving 2 effective breaths followed by chest compressions; if you are alone, continue with 5 cycles (about 2 minutes) of compressions and ventilations before calling the ambulance and (for children 1 year of age and older) getting an AED. If 2 rescuers are present, send the second rescuer to call the ambulance immediately and get an AED (if appropriate), while you continue CPR.

SUMMARY

Above mentioned discussion emphasizes the point that early institution of CPR can make a difference in the survival of children.

In the Indian scenario CPR training needs to be imparted to Police, Firefighters, swimming/sports and school instructors, general practitioners and lay public by running frequent CPR courses.

"Adapted from American Heart Association 2005 Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care."

CHAPTER

Pediatric and Neonatal Cardiopulmonary Resuscitation

Praveen Khilnani, Mritunjay Pao

PEDIATRIC ADVANCED LIFE SUPPORT

Sudden cardiac arrest in children is uncommon, more often it is the terminal event of progressive respiratory failure or shock.

RESPIRATORY FAILURE

Anticipate respiratory failure and possible respiratory arrest should be anticipated in the presence of the following: a) increased respiratory rate, particularly with signs of distress (e.g., increased effort, nasal flaring, retractions, or grunting) b) inadequate respiratory rate, effort, or chest excursion (e.g., diminished breath sounds, gasping, and cyanosis), c) especially if mental status is depressed·

SHOCK

In children the most common cause of shock is hypovolemia, (esp.hemorrhagic shock). Distributive and cardiogenic shock is seen less often. Shock results from inadequate blood flow and oxygen delivery to meet tissue metabolic demands. Signs of compensated shock include tachycardia, cool extremities, prolonged capillary refill (despite warm ambient temperature), weak peripheral pulses compared with central pulses, normal blood pressure· Uncompensated shock presents with, depressed mental status, decreased urine output, metabolic acidosis, tachypnea and weak central pulses plus hypotension. Uncompensated shock is clinically indicated by nondetectable distal pulses with weak central pulses in an infant or child with other signs and symptoms consistent with inadequate tissue oxygen delivery indicates decompensated shock.

In compensated shock, blood pressure remains normal; hypotension indicates a state of decompensated shock. Hypotension is a *systolic* blood pressure less than the 5th percentile of normal for age, and can be estimated by the following formula:

<60 mm Hg in term neonates (0 to 28 days)
<70 mm Hg in infants (1 month to 12 months)
<70 mm Hg + (2 x age in years) in children 1 to 10 years
<90 mm Hg in children 10 years of age

AIRWAY

Oropharyngeal and Nasopharyngeal Airways

Oropharyngeal and nasopharyngeal airways are adjuncts for maintaining an open airway. Oropharyngeal airways are used in unconscious victims (ie, with no gag reflex). Nasopharyngeal airways will be better tolerated than oral airways by patients who are not deeply unconscious.

Laryngeal Mask Airway

There is insufficient evidence to recommend for or against the routine use of a laryngeal mask airway during cardiac arrest. When endotracheal intubation is not possible, the LMA is an acceptable adjunct for experienced providers.

OXYGENATION AND ASSISTED VENTILATION

Oxygen

Use 100% oxygen during resuscitation. Monitor the patient's oxygen level. When the patient is stable, wean the supplementary oxygen if the oxygen saturation is maintained.

Pulse Oximetry

Monitor oxygen saturation continuously (if the patient has a perfusing rhythm), with a pulse oximeter, clinical recognition of hypoxemia is not reliable. It may be unreliable in a patient with poor peripheral perfusion.

Bag-Mask Ventilation

For short periods bag-mask ventilation can be as effective as ventilation through an endotracheal tube and may be safer, especially during short transports. Select a correct mask size, open the airway, make a tight seal between mask and face, ventilate, and assess effectiveness of ventilation. Avoid overventilation during resuscitation of victims of cardiac arrest, use only the force and tidal volume needed to make the chest rise visibly. During CPR for the patient with no advanced airway (e.g. endotracheal tube, LMA) in place, ventilation rate is determined by the compression-ventilation ratio. Single rescuers pause after 30 compressions to give 2 ventilations with mouth-to-mouth, mouth-to-mask, or bag-mask techniques and after 15 compressions to give 2 ventilations. Give each breath over 1 second.

If an advanced airway like endotracheal tube, Combitube or, LMA is in place during CPR ventilate at a rate of 8 to 10 times per minute without pausing chest compressions. In the victim with a perfusing rhythm but absent or inadequate respiratory effort, give 12 to 20 breaths per minute (use the mnemonic "squeeze-release-release" at a normal speaking rate).

Two-Person Bag-Mask Ventilation

One rescuer uses both hands to maintain an open airway with a jaw thrust and a tight mask-to-face seal while the other compresses the ventilation bag. The 2-person technique may be more effective than ventilation by a single rescuer if the patient has significant airway obstruction, poor lung compliance, or difficulty in creating a tight mask-to-face seal. Both rescuers should observe the victim's chest to ensure chest rise.

Gastric Inflation

Gastric inflation may interfere with effective ventilation and cause regurgitation. It can be minimized by avoiding excessive peak inspiratory pressures (e.g. by ventilating slowly and watching chest rise). Deliver only the volume needed to produce visible chest rise. In an unresponsive victim apply cricoid pressure. Pass a nasogastric or orogastric tube after intubating, because a gastric tube interferes with the gastroesophageal sphincter allowing possible regurgitation.

Ventilation through an Endotracheal Tube

Endotracheal intubation in infants and children requires special training because the pediatric airway anatomy differs from adult airway anatomy Complications can be minimized by the use of rapid sequence intubation (RSI).

Rapid Sequence Intubation

Experienced skilled providers may use sedatives neuromuscular blocking agents, and other medications to rapidly sedate and paralyze the victim to facilitate emergency intubation and reduce the incidence of complications. A secondary plan to manage the airway should be planned ahead in case intubation cannot be achieved.

Cuffed Versus Uncuffed Tubes

In the in-hospital setting a cuffed endotracheal tube is as safe as an uncuffed tube for infants beyond the newborn period and in children. In certain circumstances (e.g. poor lung compliance, high airway resistance, or a large glottic air leak) a cuffed tube may be preferable provided that attention is paid to endotracheal tube size, position, and cuff inflation pressure. Keep cuff inflation pressure <20 cm H_2O.

Endotracheal Tube Size

The internal diameter of the endotracheal tube for a child can be estimated for children 1 to 10 years o age, based on the child's age: Uncuffed endotrachea tube size (mm ID) = (age in years/4) + 4. Cuffed endotracheal tube size (mm ID) = (age in years/4) + 3· Uncuffed endotracheal tubes that have interna diameters that are 0.5 mm smaller and 0.5 mm large than the size estimated should also be ready at the bedside for use.

Verification of Endotracheal Tube Placement

Both clinical assessment and confirmatory devices must be used to verify proper tube placement immediately after intubation, because no single confirmation technique, including clinical signs or the presence of water vapor in the tube, is completely reliable during transport, and when the patient is moved. Immediately after intubation and again after securing the tube, confirm correct tube position with the following techniques while providing positive-pressure ventilation with a bag: bilateral chest movement and equal breath sounds over both lung fields, (especially over the axillae), gastric insufflation sounds over the stomach (they should not be present if the tube is in the trachea).

Check for exhaled CO_2 if there is a perfusing rhythm. Check oxygen saturation with a pulse oximeter. If still uncertain, perform direct laryngoscopy and look to see if the tube goes between the cords. A chest x-ray will verify that the tube is not in the right main bronchus and a high tube position is at risk of easy displacement. If an intubated patient's condition deteriorates, consider the following using the mnemonic "**DOPE**" (Displacement of the tube from the trachea' Obstruction of the tube, Pneumothorax, Equipment failure).

Exhaled or End-Tidal CO_2 Monitoring

In infants and children with a perfusing rhythm, a colorimetric detector or capnography should be used to detect exhaled CO_2 to confirm endotracheal tube position in the prehospital and in-hospital settings and during intrahospital and interhospital transport. A color change or the presence of a capnography waveform confirms tube position in the trachea but does not rule out right main bronchus intubation. During cardiac arrest, if exhaled CO_2 is not detected, confirm tube position with direct laryngoscopy because the absence of CO_2 may be a reflection of low pulmonary blood flow.

Esophageal Detector Devices

The self-inflating bulb (esophageal detector device) may be considered to confirm endotracheal tube placement in children weighing >20 kg with a perfusing rhythm. There is insufficient data to make a recommendation for or against its use in children during cardiac arrest.

Transtracheal Catheter Ventilation

Transtracheal catheter ventilation by trained personnel may be considered for support of oxygenation in the patient with severe airway obstruction if you cannot provide oxygen or ventilation any other way.

Suction Devices

Use a maximum suction force of 80 to 120 mm Hg for suctioning the airway via an endotracheal tube. Use higher suction pressures and large-bore noncollapsible suction tubing as well as semirigid pharyngeal tips to suction the mouth and pharynx.

Circulation

Push hard and push fast. Good chest compressions require an adequate compression rate (100 compressions per minute), an adequate compression depth (about one third to one half of the anterior-posterior diameter), and full recoil of the chest after each compression, and minimal interruptions in compressions.

Backboard

A firm surface that extends from the shoulders to the waist and across the full width of the bed provides optimal support for effective chest compressions. In ambulances and mobile life support units, use a spine board.

CPR: Techniques and Adjuncts

There is insufficient data to make a recommendation for or against the use of mechanical devices to compress the sternum, active compression-decompression CPR, interposed abdominal compression CPR, pneumatic antishock garment during resuscitation from cardiac arrest, and open-chest direct heart compression.

Extracorporeal Membrane Oxygenation

In centres where available, extracorporeal CPR is instituted for in-hospital cardiac arrest refractory to initial resuscitation attempts if the condition leading to cardiac arrest is reversible or amenable to heart transplantation, if excellent conventional CPR has been performed after no more than several minutes of no-flow cardiac arrest (arrest time without CPR), and if the institution is able to rapidly perform extracorporeal membrane oxygenation. Long-term survival is possible even after >50 minutes of CPR in selected patients.

Cardiovascular Monitoring

Attach electrocardiographic (ECG) monitoring leads or defibrillator pads as soon as possible and monitor blood pressure. If the patient has an indwelling arterial catheter, use the waveform to guide your technique in compressing the chest. A minor adjustment of your hand position or depth of compression can significantly improve the waveform.

Vascular Access

Vascular access is essential for administering medications and drawing blood samples. Limit the time you attempt venous access, and if you cannot achieve reliable access quickly, establish IO access. In cardiac arrest immediate IO access is recommended if no other IV access is already in place.

Intraosseous Access

IO access is a rapid, safe, and effective route for the administration of medications and fluids, and it may be used for obtaining an initial blood sample during resuscitation . You can safely administer epinephrine, adenosine, fluids, blood products, and catecholamines. Onset of action and drug levels achieved are comparable to venous administration. You can also obtain blood specimens for type and crossmatch and for chemical and blood gas analysis even during cardiac arrest, but acid-base analysis is inaccurate after sodium bicarbonate administration via the IO cannula. Use manual pressure or an infusion pump to administer viscous drugs or rapid fluid boluses, and follow each medication with a saline flush to promote entry into the central circulation.

Venous Access

A central intravenous line (IV) provides more secure long-term access, but central drug administration does not achieve higher drug levels or a substantially more rapid response than peripheral administration.

Endotracheal Drug Administration

Any vascular access, IO or IV, is preferable, but if you cannot establish vascular access, you can give lipid-soluble drugs such as lidocaine, epinephrine atropine, and naloxone ("LEAN") via the endotracheal tube, although optimal endotracheal doses are unknown. Flush with a minimum of 5 mL normal saline followed by 5 assisted manual ventilations. If CPR is in progress, stop chest compressions briefly during administration of medications. Non–lipid-soluble drugs (e.g. sodium bicarbonate and calcium) may injure the airway and should not be administered via the endotracheal route. Administration of resuscitation drugs into the trachea results in lower blood concentrations than the same dose given intravascularly.

EMERGENCY FLUIDS AND MEDICATIONS

Estimating Weight

Tapes with precalculated doses printed at various patient lengths are helpful and have been clinically validated. Hospitalized patients should have weights and precalculated emergency drug doses recorded and readily available.

Fluids

Use an isotonic crystalloid solution (e.g. lactated Ringer's solution or normal saline) to treat shock; there is no benefit in using colloid (e.g. albumin) during initial resuscitation. Use bolus therapy with a glucose-containing solution to only treat documented hypoglycemia. There is insufficient data to make a recommendation for or against hypertonic saline for shock associated with head injuries or hypovolemia.

Medications for Pediatric Resuscitation and Arrhythmias

Medication	*Dose*	*Remarks*
Adenosine	0.1 mg/kg (maximum 6 mg) Repeat: 0.2 mg/kg (maximum 12 mg) Rapid IV/IO bolus	Monitor ECG
Amiodarone	5 mg/kg IV/IO; repeat up to 15 mg/kg Maximum: 300 mg	Monitor ECG and blood pressure Adjust administration rate to urgency (give more slowly

contd..

contd...

Medication	*Dose*	*Remarks*
		when perfusing rhythm present) Use caution when administering with other drugs that prolong QT (consider expert consultation)
Atropine	0.02 mg/kg IV/IO 0.03 mg/kg ET* Repeat once if needed Minimum dose: 0.1 mg Maximum single dose: Child 0.5 mg Adolescent 1 mg	Higher doses may be used with organophosphate poisoning
Calcium chloride (10%)	20 mg/kg IV/IO (0.2 mL/kg) Adult dose: 5–10 mL	Slowly
Epinephrine	0.01 mg/kg (0.1 mL/kg 1:10 000) IV/IO May repeat q 3–5 min 0.1 mg/kg (0.1 mL/kg 1:1000) ET* Maximum dose: 1 mg IV/IO; 10 mg ET	
Glucose	0.5–1 g/kg IV/IO $D_{10}W$: 5–10 mL/kg $D_{25}W$: 2–4 mL/kg $D_{50}W$: 1–2 mL/kg	
Lidocaine	Bolus: 1 mg/kg IV/IO Maximum dose: 100 mg Infusion: 20–50 µg/kg per minute ET*: 2–3 mg	
Magnesium sulfate	25–50 mg/kg IV/IO over 10–20 min; faster in torsades, Maximum dose: 2g	
Naloxone	<5 y or 20 kg: 0.1 mg/kg IV/IO/ET* 5 y or >20 kg: 2 mg IV/IO/ET*	
Procainamide	15 mg/kg IV/IO over 30–60 min	Monitor ECG and blood pressure

Adult dose: 20 mg/min IV infusion up to total maximum dose 17 mg/kg Use caution when administering with other drugs that prolong QT (consider expert consultation)

contd...

contd...

Medication	*Dose*	*Remarks*
Sodium bicarbonate	1 mEq/kg per dose IV/IO slowly	After adequate ventilation

IV indicates intravenous; IO, intraosseous; and ET, via endotracheal tube.

*Flush with 5 mL of normal saline and follow with 5 ventilations.

PULSELESS ARREST (FIG. 3.1)

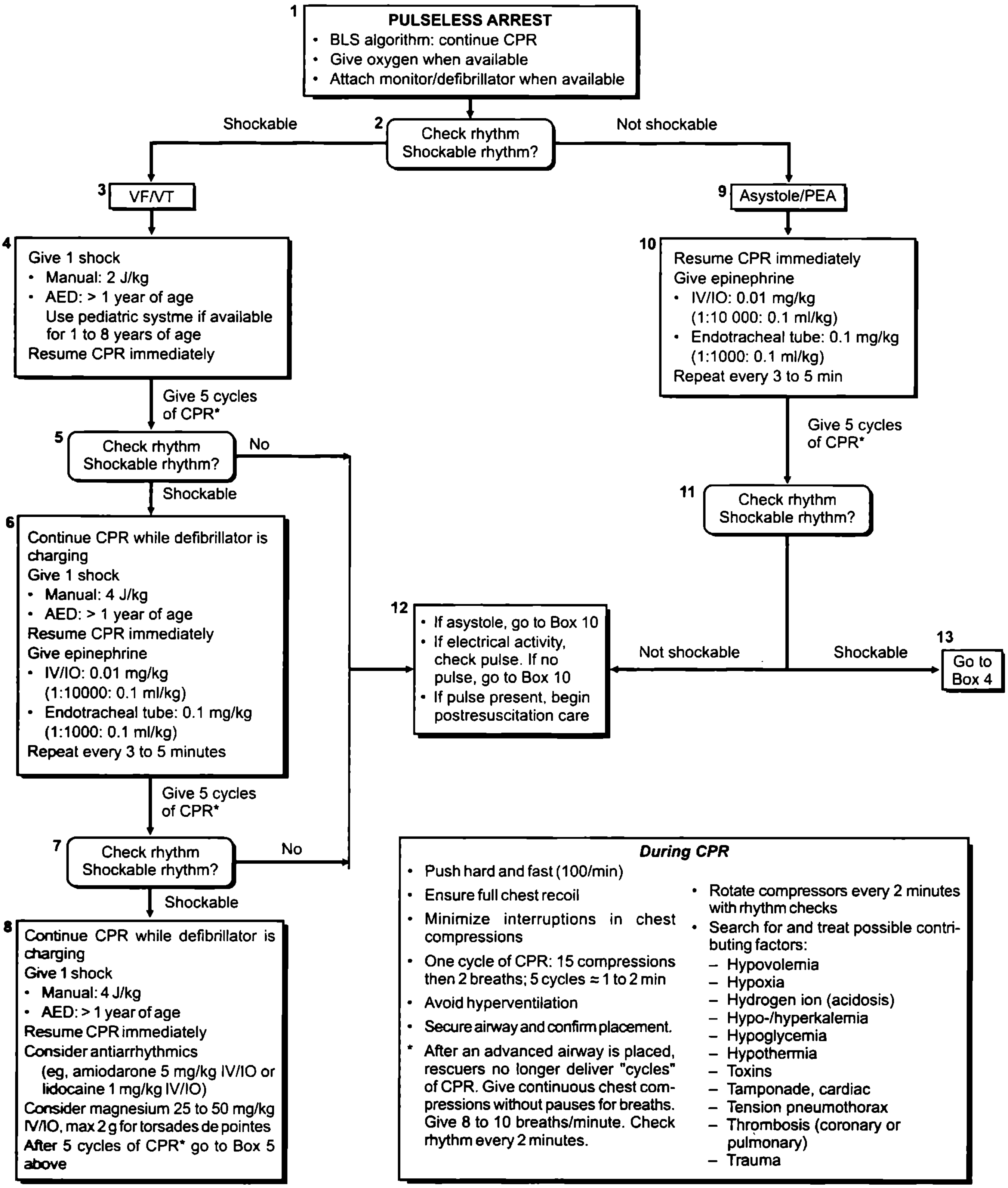
If a victim becomes unresponsive (Box 1), start CPR immediately (with supplementary oxygen if available) and send for a defibrillator (manual or automated external defibrillator [AED]). Asystole and bradycardia with a wide QRS complex are most common in asphyxial cardiac arrest. VF and pulseless electrical activity (PEA) are less common and more likely to be observed in children with sudden arrest. If you are using an ECG monitor, determine the rhythm (Box 2); if you are using an AED, the device will tell you whether the rhythm is "shockable" (i.e. VF or rapid VT), but it may not display the rhythm.

"Shockable Rhythm": VF/Pulseless VT

VF occurs in 5% to 15% of all pediatric victims of out-of-hospital cardiac arrest and is reported in up to 20% of pediatric in-hospital arrests at some point during the resuscitation. The incidence increases with age. Defibrillation is the definitive treatment for VF (Class I) with an overall survival rate of 17% to 20%, but in adults the probability of survival declines by 7% to 10% for each minute of arrest without CPR and defibrillation. The decline in survival is more gradual when early CPR is provided.

Defibrillators

Defibrillators are either manual or automated (AED), with monophasic or biphasic waveforms. Institutions that care for children at risk for arrhythmias and cardiac arrest (e.g. hospitals, emergency departments) ideally should have defibrillators available that are capable of energy adjustment that is appropriate for children. Many AED parameters are set automatically. Use the largest paddles or self-adhering electrodes that will fit on the chest wall



1 **PULSELESS ARREST**
- BLS algorithm: continue CPR
- Give oxygen when available
- Attach monitor/defibrillator when available

2 Check rhythm
Shockable rhythm?

3 VF/VT

4 Give 1 shock
- Manual: 2 J/kg
- AED: > 1 year of age
  Use pediatric systme if available
  for 1 to 8 years of age

Resume CPR immediately

5 Check rhythm
Shockable rhythm?

6 Continue CPR while defibrillator is charging
Give 1 shock
- Manual: 4 J/kg
- AED: > 1 year of age

Resume CPR immediately
Give epinephrine
- IV/IO: 0.01 mg/kg
  (1:10000: 0.1 ml/kg)
- Endotracheal tube: 0.1 mg/kg
  (1:1000: 0.1 ml/kg)

Repeat every 3 to 5 minutes

7 Check rhythm
Shockable rhythm?

8 Continue CPR while defibrillator is charging
Give 1 shock
- Manual: 4 J/kg
- AED: > 1 year of age

Resume CPR immediately
Consider antiarrhythmics
(eg, amiodarone 5 mg/kg IV/IO or lidocaine 1 mg/kg IV/IO)
Consider magnesium 25 to 50 mg/kg IV/IO, max 2 g for torsades de pointes
After 5 cycles of CPR* go to Box 5 above

9 Asystole/PEA

10 Resume CPR immediately
Give epinephrine
- IV/IO: 0.01 mg/kg
  (1:10 000: 0.1 ml/kg)
- Endotracheal tube: 0.1 mg/kg
  (1:1000: 0.1 ml/kg)

Repeat every 3 to 5 min

11 Check rhythm
Shockable rhythm?

12
- If asystole, go to Box 10
- If electrical activity, check pulse. If no pulse, go to Box 10
- If pulse present, begin postresuscitation care

13 Go to Box 4

During CPR
- Push hard and fast (100/min)
- Ensure full chest recoil
- Minimize interruptions in chest compressions
- One cycle of CPR: 15 compressions then 2 breaths; 5 cycles ≈ 1 to 2 min
- Avoid hyperventilation
- Secure airway and confirm placement.

* After an advanced airway is placed, rescuers no longer deliver "cycles" of CPR. Give continuous chest compressions without pauses for breaths. Give 8 to 10 breaths/minute. Check rhythm every 2 minutes.

- Rotate compressors every 2 minutes with rhythm checks
- Search for and treat possible contributing factors:
  - Hypovolemia
  - Hypoxia
  - Hydrogen ion (acidosis)
  - Hypo-/hyperkalemia
  - Hypoglycemia
  - Hypothermia
  - Toxins
  - Tamponade, cardiac
  - Tension pneumothorax
  - Thrombosis (coronary or pulmonary)
  - Trauma

Fig. 3.1: Pulseless arrest algorithm

without touching (leave about 3 cm between the paddles). Adult paddles (8 to 10 cm) for children >10 kg (more than approximately 1 year of age). Infant paddles for infants weighing <10 kg . The electrode–chest wall interface can be gel pads, electrode cream, paste, or self-adhesive monitoring-defibrillation pads. Apply firm pressure on the paddles (manual) placed over the right side of the upper chest and the apex of the heart (to the left of the nipple over the left lower ribs). Alternatively place one electrode on the front of the chest just to the left of the sternum and the other over the upper back below the scapula.

Energy Dose

The lowest energy dose for effective defibrillation and the upper limit for safe defibrillation in infants and children are not known. Biphasic shocks appear to be at least as effective as monophasic shocks and less harmful. With a manual defibrillator (monophasic or biphasic), use a dose of 2 J/kg for the first attempt and 4 J/kg for subsequent attempts.

AEDs

Many AEDs can accurately detect VF in children of all ages and differentiate shockable from non-shockable rhythms with a high degree of sensitivity and specificity. AEDs can be safely and effectively used in children 1 to 8 years of age. There is insufficient data to make a recommendation for or against using an AED in infants <1 year of age. When using an AED for children about 1 to 8 years old, use a pediatric attenuator system, which decreases the delivered energy to a dose suitable for children. If an AED with a pediatric attenuating system is not available, use a standard AED, preferably one with sensitivity and specificity for pediatric shockable rhythms.

Defibrillation Sequence

If VF or Pulseless VT is present, follow the following steps:

1. Attempt defibrillation immediately. The earlier you attempt defibrillation, the more likely the attempt will be successful.
2. Provide CPR until the defibrillator is ready to deliver a shock.
3. Give first shock (2 J/kg) as quickly as possible and immediately resume CPR, beginning with chest compressions (Box 4). If 1 shock fails to eliminate VF, the incremental benefit of another shock is low, and resumption of CPR is likely to confer a greater value than another shock. CPR may provide some coronary perfusion with oxygen and substrate delivery, increasing the likelihood of defibrillation with a subsequent shock. Check the rhythm. Continue CPR for about 5 cycles (about 2 minutes).
4. Check the rhythm (Box 5). If a shockable rhythm persists, give second shock (4 J/kg), resume compressions immediately. Give a dose of epinephrine. Use a standard dose of epinephrine (.01mg/kg) for the first and subsequent doses. There is no survival benefit from routine use of high-dose epinephrine, and it may be harmful, particularly in asphyxia. Give the standard dose of epinephrine about every 3 to 5 minutes during cardiac arrest.
5. After 5 cycles (approximately 2 minutes) of CPR, check the rhythm (Box 7). If the rhythm continues to be "shockable," deliver a shock (4 J/kg), resume CPR (beginning with chest compressions) immediately, and give amiodarone or lidocaine. Continue CPR for 5 cycles (about 2 minutes) before again checking the rhythm and attempting to defibrillate if needed with 4 J/kg.
6. Once an advanced airway is in place, the compressing rescuer should give continuous chest compressions at a rate of 100 per minute without pauses for ventilation. The rescuer delivering ventilation provides 8 to 10 breaths per minute. Two or more rescuers should rotate the compressor role approximately every 2 minutes to prevent compressor fatigue and deterioration in quality and rate of chest compressions.
7. If you have a monitor or an AED with a rhythm display and there is an organized rhythm at any time, check for a pulse and proceed accordingly.
8. If defibrillation is successful but VF recurs, continue CPR while you give another bolus of amiodarone before you try to defibrillate with the previously successful shock dose (see Box 8).
9. Search for and treat reversible causes (see green "During CPR" box).

Torsades de Pointes

This polymorphic VT is seen in patients with a long QT interval, which may be congenital or may result from toxicity with type IA antiarrhythmics (e.g. procainamide, quinidine, and disopyramide) or type III antiarrhythmics (e.g. sotalol and amiodarone), tricyclic antidepressants (see below), digitalis, or drug interactions. These are examples of contributing factors listed in the green box in the algorithm.

Treatment

Regardless of the cause, treat torsades de pointes with a rapid (over several minutes) IV infusion of magnesium sulfate.

ASYSTOLE/PEA: "nonshockable rhythm"

The most common ECG findings in infants and children in cardiac arrest are asystole and PEA. PEA is organized electrical activity—most commonly slow, wide QRS. For asystole and PEA resume CPR and continue with as few interruptions in chest compressions as possible. A second rescuer gives epinephrine while the first continues CPR. Use a standard dose for the first and subsequent doses. High-dose epinephrine may be considered in exceptional circumstances such as β-blocker overdose. Search for and treat reversible causes.

BRADYCARDIA (FIG. 3.2)

The emergency treatment of bradycardia depends on its hemodynamic consequences. In patients with bradycardia that is causing cardiorespiratory compromise:

1. Support airway, breathing, and circulation as needed, administer oxygen, and attach a monitor/defibrillator.
2. If pulses, perfusion, and respirations are normal, no emergency treatment is necessary. Monitor and proceed with evaluation.
3. If heart rate remains <60 beats per minute with poor perfusion despite effective ventilation with oxygen, start chest compressions.
4. Reevaluate the patient to determine if signs of hemodynamic compromise persist despite the support of adequate oxygenation and ventilation and compressions if indicated. Verify that the support is adequate—e.g. check airway and oxygen source and effectiveness of ventilation.
5. Continue to support airway, ventilation, oxygenation (and provide compressions as needed) and give epinephrine. If bradycardia persists or responds only transiently, consider a continuous infusion of epinephrine or isoproterenol. If bradycardia is due to vagal stimulation, give atropine.
6. Emergency transcutaneous pacing may be lifesaving if the bradycardia is due to complete heart block or sinus node dysfunction unresponsive to ventilation, oxygenation, chest compressions, and medications, especially if it is associated with congenital or acquired heart disease. Pacing is not useful for asystole or bradycardia due to postarrest hypoxic/ischemic myocardial insult or respiratory failure.

TACHYCARDIA AND HEMODYNAMIC INSTABILITY (FIG. 3.3)

If pulses are palpable and the patient has signs of hemodynamic compromise (poor perfusion, tachypnea, and weak pulses), ensure that the airway is patent, assist ventilations if necessary, administer supplementary oxygen, and attach an ECG monitor or defibrillator. Assess QRS duration: determine if the QRS duration is 0.08 second (narrow-complex tachycardia) or >0.08 second (wide-complex tachycardia).

Narrow-Complex (0.08 Second) Tachycardia

Evaluation of a 12-lead ECG and the patient's clinica presentation and history differentiates probable sinus tachycardia from probable supraventricular tachycardia (SVT). If the rhythm is sinus tachycardia search for and treat reversible causes.

Probable Supraventricular Tachycardia

Monitor rhythm during therapy to evaluate effect The choice of therapy depends on the patient' degree of hemodynamic instability.

1. Attempt *vagal stimulation* first unless the patien is very unstable and if it does not unduly delay chemical or electrical cardioversion. In infants and young children, apply ice to the face withou occluding the airway. In older children, carotid sinus massage or Valsalva maneuvers are saf (have the child blow through an obstructed

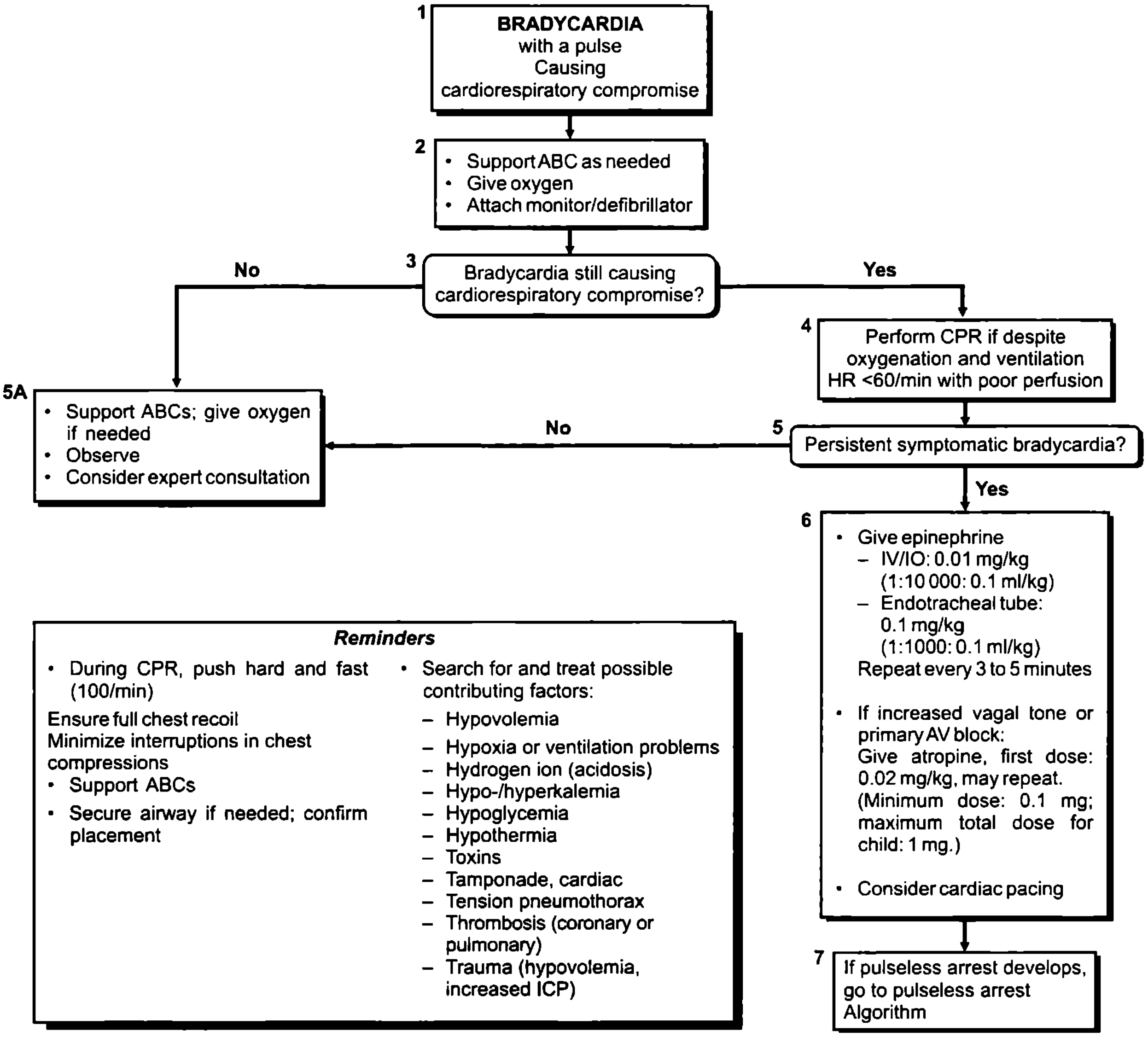

1
BRADYCARDIA
with a pulse
Causing
cardiorespiratory compromise
2
• Support ABC as needed
• Give oxygen
• Attach monitor/defibrillator
3
Bradycardia still causing cardiorespiratory compromise?
No
Yes
4
Perform CPR if despite oxygenation and ventilation HR <60/min with poor perfusion
5A
• Support ABCs; give oxygen if needed
• Observe
• Consider expert consultation
No
5
Persistent symptomatic bradycardia?
Yes
6
• Give epinephrine
– IV/IO: 0.01 mg/kg (1:10 000: 0.1 ml/kg)
– Endotracheal tube: 0.1 mg/kg (1:1000: 0.1 ml/kg)
Repeat every 3 to 5 minutes
• If increased vagal tone or primary AV block: Give atropine, first dose: 0.02 mg/kg, may repeat. (Minimum dose: 0.1 mg; maximum total dose for child: 1 mg.)
• Consider cardiac pacing
7
If pulseless arrest develops, go to pulseless arrest Algorithm
Reminders
• During CPR, push hard and fast (100/min)
Ensure full chest recoil
Minimize interruptions in chest compressions
• Support ABCs
• Secure airway if needed; confirm placement
• Search for and treat possible contributing factors:
– Hypovolemia
– Hypoxia or ventilation problems
– Hydrogen ion (acidosis)
– Hypo-/hyperkalemia
– Hypoglycemia
– Hypothermia
– Toxins
– Tamponade, cardiac
– Tension pneumothorax
– Thrombosis (coronary or pulmonary)
– Trauma (hypovolemia, increased ICP)

Fig. 3.2: Bradycardia algorithm

straw). Avoid pressure to the eye because this can damage the retina.

2. If there is no response to vagal maneuvers or if the patient is unstable use chemical cardioversion with adenosine (very effective). Administer adenosine using 2 syringes connected to a T-connector or stopcock; give adenosine rapidly with one syringe and immediately flush with 5 mL of normal saline with the other.
3. If IV access is not readily available, provide electrical (synchronized) cardioversion. Consider sedation if possible. Start with a dose of 0.5 to 1 J/kg. If unsuccessful, repeat using a dose of 2 J/kg. If a second shock is unsuccessful or the tachycardia recurs quickly, consider antiarrhythmic therapy (amiodarone or procainamide) before a third shock.
4. Consider amiodarone or procainamide for SVT unresponsive to vagal maneuvers and adenosine. Use extreme caution when administering more than one drug that causes QT prolongation (e.g. amiodarone and procainamide). Consider obtaining expert consultation. Give an infusion of amiodarone or procainamide slowly (over several minutes to an hour), depending on the urgency, while you monitor the ECG and blood

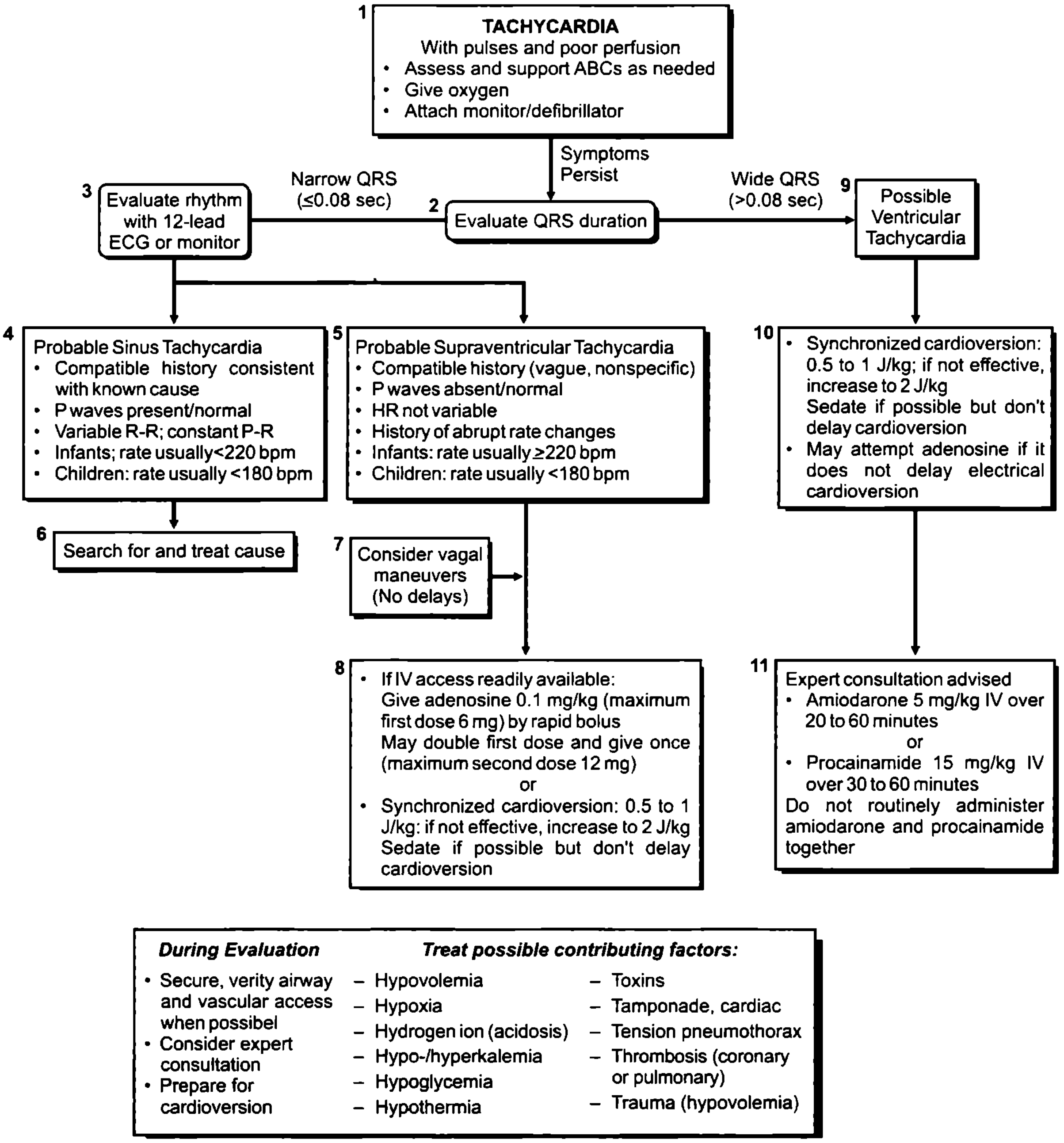

1
TACHYCARDIA
With pulses and poor perfusion
• Assess and support ABCs as needed
• Give oxygen
• Attach monitor/defibrillator
Symptoms Persist
2
Evaluate QRS duration
Narrow QRS (≤0.08 sec)
Wide QRS (>0.08 sec)
3
Evaluate rhythm with 12-lead ECG or monitor
9
Possible Ventricular Tachycardia
4
Probable Sinus Tachycardia
• Compatible history consistent with known cause
• P waves present/normal
• Variable R-R; constant P-R
• Infants; rate usually<220 bpm
• Children: rate usually <180 bpm
5
Probable Supraventricular Tachycardia
• Compatible history (vague, nonspecific)
• P waves absent/normal
• HR not variable
• History of abrupt rate changes
• Infants: rate usually ≥220 bpm
• Children: rate usually <180 bpm
10
• Synchronized cardioversion: 0.5 to 1 J/kg; if not effective, increase to 2 J/kg
Sedate if possible but don't delay cardioversion
• May attempt adenosine if it does not delay electrical cardioversion
6
Search for and treat cause
7
Consider vagal maneuvers (No delays)
8
• If IV access readily available:
Give adenosine 0.1 mg/kg (maximum first dose 6 mg) by rapid bolus
May double first dose and give once (maximum second dose 12 mg)
or
• Synchronized cardioversion: 0.5 to 1 J/kg: if not effective, increase to 2 J/kg
Sedate if possible but don't delay cardioversion
11
Expert consultation advised
• Amiodarone 5 mg/kg IV over 20 to 60 minutes
or
• Procainamide 15 mg/kg IV over 30 to 60 minutes
Do not routinely administer amiodarone and procainamide together
During Evaluation
• Secure, verity airway and vascular access when possibel
• Consider expert consultation
• Prepare for cardioversion
Treat possible contributing factors:
– Hypovolemia
– Hypoxia
– Hydrogen ion (acidosis)
– Hypo-/hyperkalemia
– Hypoglycemia
– Hypothermia
– Toxins
– Tamponade, cardiac
– Tension pneumothorax
– Thrombosis (coronary or pulmonary)
– Trauma (hypovolemia)

Fig. 3.3: Tachycardia and hemodynamic instability algorithm

pressure. If there is no effect and there are no signs of toxicity, give additional doses. Do not use verapamil in infants because it may cause refractory hypotension and cardiac arrest, and use with caution in children because it may cause hypotension and myocardial depression.

Wide-Complex (> 0.08 Second) Tachycardia

Wide-complex tachycardia with poor perfusion i probably ventricular in origin but may be supra ventricular with aberrancy. Treat with synchronize electrical cardioversion (0.5 J to 1 J/kg). If it doe not delay cardioversion, try a dose of adenosine first to determine if the rhythm is SVT with aberrant conduction. If a second shock (2 J/kg) is unsuccessful or if the tachycardia recurs quickly, consider antiarrhythmic therapy (amiodarone or procainamide) before a third shock.

Tachycardia with Hemodynamic Stability

For VT, give an infusion of amiodarone slowly (minutes to an hour depending on the urgency) while you monitor the ECG and blood pressure. If there is no effect and there are no signs of toxicity, give additional doses. If amiodarone is not available, consider giving procainamide slowly (over 30 to 60 minutes) while you monitor the ECG and blood pressure. Do not administer amiodarone and procainamide together without expert consultation. Because all arrhythmia therapies have the potential for serious adverse effects, consider consulting an expert in pediatric arrhythmias before treating children who are hemodynamically stable.

SPECIAL RESUSCITATION SITUATIONS

Trauma

If spinal injury is suspected, restrict motion of the cervical spine and avoid traction or movement of the head and neck. Open and maintain the airway with a jaw thrust, and do not tilt the head. If you cannot open the airway with a jaw thrust, use head tilt–chin lift, because you must establish a patent airway. Because of the disproportionately large head size in infants and young children, optimal positioning may require recessing the occiput or elevating the torso to avoid undesirable backboard-induced cervical flexion. Do not overventilate, brief hyperventilation may be used as a temporizing rescue therapy in the presence of signs of impending brain herniation (e.g. sudden rise in measured intracranial pressure, dilated pupil[s] not responsive to light, bradycardia, hypertension). Suspect thoracic injury in all thoracoabdominal trauma, even in the absence of external injuries. Tension pneumothorax, hemothorax, or pulmonary contusion may impair breathing.

If the patient has maxillofacial trauma or if you suspect a basilar skull fracture, insert an orogastric rather than a nasogastric tube. Treat signs of shock with a bolus of 20 mL/kg of an isotonic crystalloid (e.g. normal saline or lactated Ringer's solution) even if blood pressure is normal. Give additional boluses (20 mL/kg) if systemic perfusion fails to improve. If signs of shock persist after administration of 40 to 60 mL/kg of isotonic crystalloid, give 10 to 15 mL/kg of blood. Although type-specific crossmatched blood is preferred, in an emergency use O-negative blood in females and O-positive or O-negative in males. If possible warm the blood before rapid infusion. Consider intra-abdominal hemorrhage, tension pneumothorax, pericardial tamponade, spinal cord injury in infants and children, and intracranial hemorrhage in infants with signs of shock.

Children with Special Health Care Needs

Children with special health care needs may require emergency care for their chronic conditions (e.g. obstruction of a tracheostomy), failure of support technology (e.g. ventilator failure), progression of their underlying disease, or events unrelated to those special needs.

Ventilation with a Tracheostomy or Stoma

Parents and providers should be able to provide ventilation via the tracheostomy tube and verify effectiveness by chest expansion. If you cannot ventilate after suctioning the tube, replace it. If a clean tube is unavailable, perform mouth-to-stoma or mask-to-stoma ventilations. If the upper airway is patent, you may be able to provide effective bag-mask ventilation through the nose and mouth while you or someone else occludes the tracheal stoma.

POSTRESUSCITATION STABILIZATION

The goals of postresuscitation care are to preserve brain function, avoid secondary organ injury, diagnose and treat the cause of illness, and enable the patient to arrive at a pediatric tertiary-care facility in an optimal physiological state. Reassess frequently because cardiorespiratory status may deteriorate.

Respiratory System

Continue supplementary oxygen until you confirm adequate blood oxygenation and oxygen delivery. Monitor by continuous pulse oximetry. Intubate and mechanically ventilate the patient if there is significant respiratory compromise (tachypnea, respiratory distress with agitation or decreased responsiveness, poor air exchange, cyanosis, hypoxemia). If the patient is already intubated, verify tube position, patency, and security. In the hospital setting, obtain arterial blood gases 10 to 15 minutes after establishing the initial ventilatory settings and make appropriate adjustments. Ideally correlate blood gases with capnographic end-tidal CO_2 concentration to enable noninvasive monitoring of ventilation.

Cardiovascular System

Continuously monitor heart rate, blood pressure (by direct arterial line if possible), and oxygen saturation. Myocardial dysfunction is common after cardiac arrest. Systemic and pulmonary vascular resistance is increased except in some cases of septic shock. Vasoactive agents may improve hemodynamics, but each drug and dose must be tailored to the patient because clinical response is variable. Infuse all vasoactive drugs into a secure IV line. The potential adverse effects of catecholamines include local ischemia and ulceration, tachycardia, atrial and ventricular tachyarrhythmias, hypertension, and metabolic changes (hyperglycemia, increased lactate concentration, and hypokalemia).

Neurologic System

Do not provide routine hyperventilation. Brief hyperventilation may be used in the presence of signs of impending cerebral herniation (e.g. sudden rise in measured intracranial pressure, dilated pupil[s] not responsive to light, bradycardia, hypertension). When patients remain comatose after resuscitation, consider cooling them to a temperature of 32°C to 34°C for 12 to 24 hours because cooling may aid brain recovery. The ideal method and duration of cooling and rewarming are not known. Prevent shivering by providing sedation and, if needed, neuromuscular blockade. Complications of hypothermia include infection, diminished cardiac output, arrhythmia, pancreatitis, coagulopathy, thrombocytopenia, hypophosphatemia, and hypomagnesemia. Neuromuscular blockade can mask seizures. Monitor temperature and treat fever aggressively with antipyretics and cooling devices because fever adversely influences recovery from ischemic brain injury. Treat postischemic seizures aggressively; search for a correctable metabolic cause such as hypoglycemia or electrolyte imbalance.

Renal System

Decreased urine output (<1 mL/kg per hour in infants and children or <30 mL/h in adolescents) may be caused by prerenal conditions (e.g. dehydration, inadequate systemic perfusion), renal ischemic damage, or a combination of factors. Avoid nephrotoxic medications and adjust the dose of medications excreted by the kidneys until you have checked renal function.

Interhospital Transport

Transport team members should be trained and experienced in the care of critically ill and injured children and supervised by a pediatric emergency medicine or pediatric critical care physician. The mode of transport and composition of the team should be established for each system based on the care required by an individual patient. Monitor exhaled CO_2 (qualitative colorimetric detector or capnography) during interhospital or intrahospital transport of intubated patients. The following recommendations are relevant to the western scenario but may not apply in the Indian scenario.

Family Presence during Resuscitation

Most family members would like to be present during resuscitation. Parents and care providers of chronically ill children are often knowledgeable about and comfortable with medical equipment and emergency procedures. Family members with no medical background report that being at the side of a loved one and saying goodbye during the final moments of life is comforting and helps in their adjustment, and most would participate again. Standardized psychological examinations suggest that, compared with those not present, family members who were present during attempted resuscitation have less anxiety and depression and more constructive grieving behavior.Parents or family members often fail to ask, but health care providers should offer the opportunity whenever possible. If the presence of family members proves detrimental to the resuscitation, they should be gently asked to leave. Members of the resuscitation team must be sensitive to the presence of family members, and one person should be assigned to comfort, answer questions, and discuss the needs of the family.

Termination of Resuscitative Efforts Family Presence during Resuscitation

Unfortunately there are no reliable predictors of outcome during resuscitation to guide when to terminate resuscitative efforts. Witnessed collapse, bystander CPR, and a short time interval from collapse to arrival of professionals improve the chances of a successful resuscitation. In the past, children who underwent prolonged resuscitation and absence of return of spontaneous circulation after 2 doses of epinephrine were considered unlikely to survive, but intact survival after unusually prolonged in-hospital resuscitation has been documented. Prolonged efforts should be made for infants and children with recurring or refractory VF or VT, drug toxicity, or a primary hypothermic insult.

NEONATAL RESUSCITATION

Although the vast majority of newly born infants do not require intervention to make the transition from intrauterine to extrauterine life, because of the large number of births, a sizable number will require some degree of resuscitation.

Rapidly asses if the baby is 1) born after a full-term gestation, 2) has a normal cry and breathing, 3) good muscle tone, 4) and clear of meconium and no evidence of infection, if the answer is "Yes" no resuscitation is required. The baby should be dried, placed directly on the mother's chest, and covered with dry linen to maintain temperature. A newly born infant who is uncompromised will achieve and maintain pink mucous membranes without administration of supplementary oxygen. Observation of breathing, activity, and color should be ongoing.

If the answer to any of these assessment questions is "no," than the infant should receive one or more of the following 4 categories of action in sequence: A.) Initial steps in stabilization (provide warmth, position, clear airway, dry, stimulate, reposition) B.) Ventilation, C.) Chest compressions, D.) Administration of epinephrine and/or volume expansion·

The decision to progress from one category to the next is determined by the simultaneous assessment of 3 vital signs: 1) Respirations, 2) Heart rate, and 3) Color. Approximately 30 seconds is allotted to complete each step, reevaluate, and decide whether to progress to the next step (see the Figure 3.4)

ANTICIPATION OF RESUSCITATION NEED

With careful consideration of risk factors, the majority of newborns who will need resuscitation can be identified before birth. If the possible need for resuscitation is anticipated, additional skilled personnel capable of initiating resuscitation, including administration of positive-pressure ventilation and chest compressions should be present and the necessary equipment prepared. If a preterm delivery (<37 weeks of gestation) is expected, special preparations will be required. Preterm babies have immature lungs that may be more difficult to ventilate and are also more vulnerable to injury by positive-pressure ventilation. Preterm babies also have immature blood vessels in the brain that are prone to hemorrhage; thin skin and a large surface area, which contribute to rapid heat loss; increased susceptibility to infection; and increased risk of hypovolemic shock caused by small blood volume.

INITIAL STEPS

The initial steps of resuscitation are to provide warmth by placing the baby under a radiant heat source, position the head in a "sniffing" position to open the airway, clear the airway with a bulb syringe or suction catheter, and dry the baby and stimulate breathing. Recent studies have examined several aspects of these initial steps. These studies are summarized below.

Temperature Control

Very low birth weight (<1500 g) preterm babies are likely to become hypothermic despite the use of traditional techniques for decreasing heat loss. For them additional warming techniques be used, such as covering the baby in plastic wrapping (food-grade, heat-resistant plastic) and placement under radiant

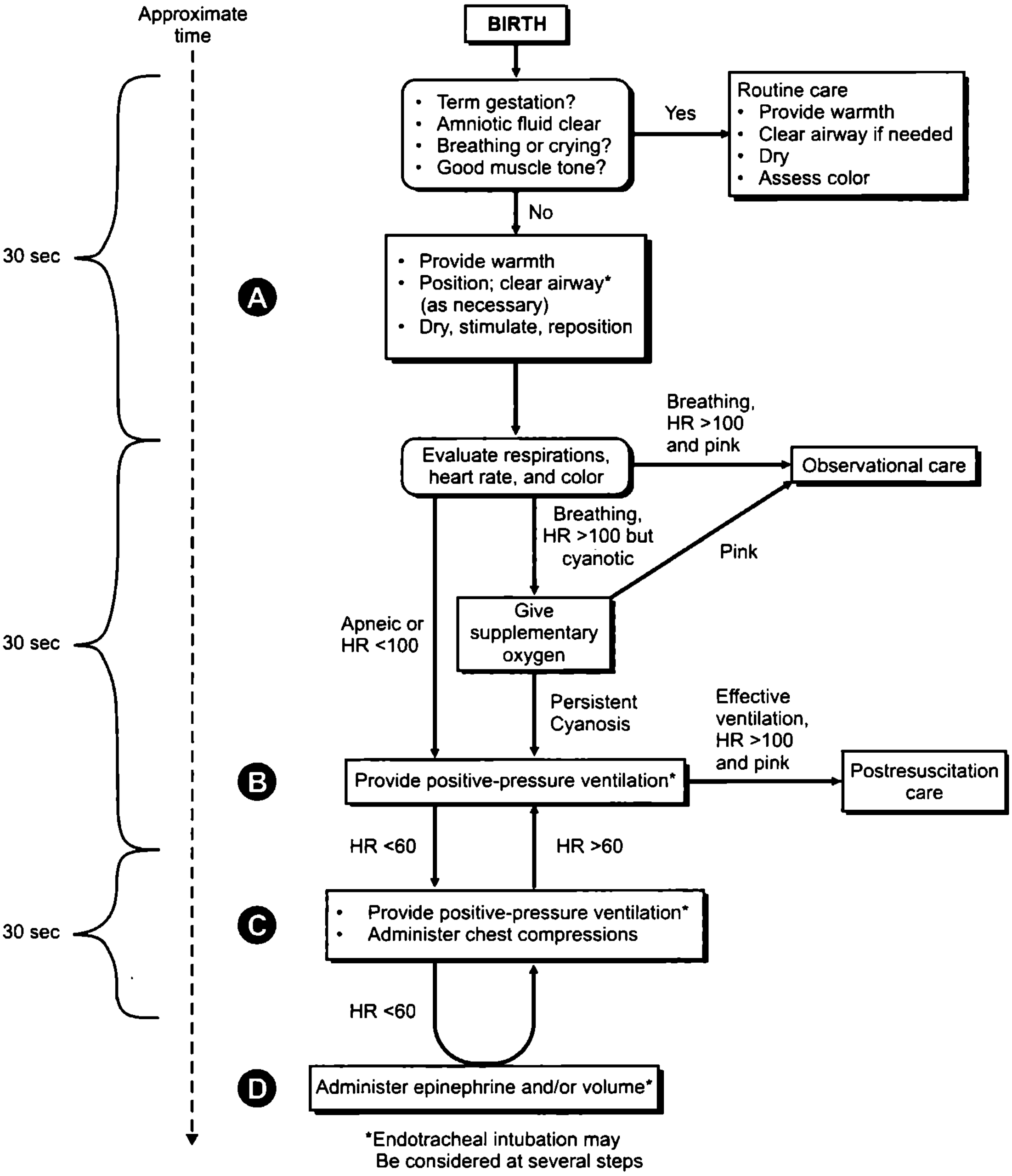

Approximate time
BIRTH
Term gestation?
Amniotic fluid clear
Breathing or crying?
Good muscle tone?
Yes
Routine care
Provide warmth
Clear airway if needed
Dry
Assess color
No
30 sec
A
Provide warmth
Position; clear airway* (as necessary)
Dry, stimulate, reposition
Breathing, HR >100 and pink
Evaluate respirations, heart rate, and color
Observational care
Breathing, HR >100 but cyanotic
Pink
Apneic or HR <100
Give supplementary oxygen
30 sec
Persistent Cyanosis
Effective ventilation, HR >100 and pink
B
Provide positive-pressure ventilation*
Postresuscitation care
HR <60
HR >60
30 sec
C
Provide positive-pressure ventilation*
Administer chest compressions
HR <60
D
Administer epinephrine and/or volume*
*Endotracheal intubation may Be considered at several steps

Fig. 3.4: Algorithm for neonatal resuscitation

heat. Temperature must be monitored closely because of the slight but described risk of hyperthermia with this technique. Other techniques to maintain temperature during stabilization of the baby in the delivery room (e.g. drying and swaddling, warming pads, increased environmental temperature, placing the baby skin-to-skin with the mother and covering both with a blanket) have been used, but they have not been evaluated in controlled trials nor compared with the plastic wrap technique for premature babies. All resuscitation procedures, including endotracheal intubation, chest compression, and insertion of lines, can be performed with these temperature-controlling interventions in place.

Infants born to febrile mothers have been reported to have a higher incidence of perinatal respiratory depression, neonatal seizures, and cerebral palsy and increased risk of mortality.

Hyperthermia during or after ischemia is associated with progression of cerebral injury, so hyperthermia should be avoided. The goal is to achieve normothermia and avoid iatrogenic hyperthermia.

Clearing the Airway of Meconium

Current recommendations no longer advise routine intrapartum oropharyngeal and nasopharyngeal suctioning for infants born to mothers with meconium staining of amniotic fluid. Endotracheal intubation of meconium-stained infants immediately following birth and suction applied to the endotracheal tube as it is withdrawn offers no benefit if the infant is vigorous [one who has strong respiratory efforts, good muscle tone, and a heart rate >100 beats per minute (bpm)]. Endotracheal suctioning for infants who are not vigorous should be performed immediately after birth.

Periodic Evaluation at 30-Second Intervals

After the immediate post birth assessment and administration of initial steps, further resuscitative efforts should be guided by simultaneous assessment of respirations, heart rate, and color. After initial respiratory efforts the newly born infant should be able to establish regular respirations that are sufficient to improve color and maintain a heart rate >100 bpm. Gasping and apnea indicate the need for assisted ventilation. Increasing or decreasing heart rate can also provide evidence of improvement or deterioration. Central cyanosis is determined by examining the face, trunk, and mucous membranes. Acrocyanosis (blue color of hands and feet alone) is usually a normal finding at birth and is not a reliable indicator of hypoxemia but may indicate other conditions, such as cold stress. Pallor or mottling may be a sign of decreased cardiac output, severe anemia, hypovolemia, hypothermia, or acidosis.

Administration of Oxygen

Whenever positive-pressure ventilation is indicated for resuscitation use of supplementary oxygen is recommended. Free-flow oxygen should be administered to babies who are breathing but have central cyanosis. The standard approach to resuscitation is to use 100% oxygen. If the clinician begins resuscitation with room air, it is recommended that supplementary oxygen be available to use if there is no appreciable improvement within 90 seconds after birth. In situations where supplementary oxygen is not readily available, positive-pressure ventilation should be administered with room air. Administration of a variable concentration of oxygen guided by pulse oximetry may improve the ability to achieve normoxia more quickly. Concerns about potential oxidant injury should caution the clinician about the use of excessive oxygen, especially in the premature infant.

Positive-Pressure Ventilation

If the infant remains apneic or gasping, if the heart rate remains <100 bpm 30 seconds after administering the initial steps, or if the infant continues to have persistent central cyanosis despite administration of supplementary oxygen, start positive-pressure ventilation.

Initial Breaths and Assisted Ventilation

In term infants, initial inflations (spontaneous or assisted)create a functional residual capacity. Assisted ventilation should be delivered at a rate of 40 to 60 breaths per minute to promptly achieve or maintain a heart rate >100 bpm. Adequacy of initial ventilation is indicated by prompt improvement in heart rate. The initial peak inflating pressures needed are variable and unpredictable and should be individualized to achieve an increase in heart rate and/or movement of the chest with each breath. If pressure is not monitored, the minimum inflation required to achieve an increase in heart rate should be used.

Devices used for Assisted Ventilation

A self-inflating bag, a flow-inflating bag, or a T-piece can be used to ventilate a newborn. Laryngeal mask airways (LMAs) that fit over the laryngeal inlet have been shown to be effective for ventilating newly born near-term and full-term infants. There is insufficient evidence to support the routine use of the LMA as the primary airway device during neonatal resuscitation, in the setting of meconium-stained amniotic fluid, when chest compressions are required, in very low birth weight babies, or for delivery of emergency intratracheal medications.

Assisted Ventilation of Preterm Infants

Avoid excessive chest wall movement may indicate large-volume lung inflations, while ventilating preterm infants after birth, as preterm lungs are easily injured. Monitoring of pressure may help to provide consistent inflations and avoid unnecessary high pressures. If positive-pressure ventilation is required, an initial inflation pressure of 20 to 25 cm H2O is adequate for most preterm infants. If prompt improvement in heart rate or chest movement is not obtained, higher pressures may be needed. If it is necessary to continue positive-pressure ventilation, application of PEEP may be beneficial (protects against lung injury and improves lung compliance and gas exchange). Continuous positive airway pressure in spontaneously breathing preterm infants after resuscitation may also be beneficial.

Endotracheal Tube Placement

Indications for Endotracheal intubation during neonatal resuscitation:

1. When tracheal suctioning for meconium is required
2. If bag-mask ventilation is ineffective or prolonged
3. When chest compressions are performed
4. When endotracheal administration of medications is desired
5. For special resuscitation circumstances, such as congenital diaphragmatic hernia or extremely low birth weight (<1000 g)

The best indicator that the tube is in the tracheobronchial tree is a prompt increase in heart rate. Exhaled CO2 detection is the method of choice for confirmation of endotracheal tube placement in infants, including very low birth weight infants.

CHEST COMPRESSIONS

Chest compressions are indicated for a heart rate that is <60 bpm despite adequate ventilation with supplementary oxygen for 30 seconds. Compressions should be delivered on the lower third of the sternum to a depth of approximately one third of the anterior-posterior diameter of the chest. Because ventilation is the most effective action in neonatal resuscitation and because chest compressions are likely to compete with effective ventilation, rescuers should ensure that assisted ventilation is being delivered optimally before starting chest compressions.

The 2 thumb–encircling hands technique may generate higher peak systolic and coronary perfusion pressure than the 2-finger technique, the 2 thumb–encircling hands technique is recommended for performing chest compressions in newly born infants. However, the 2-finger technique may be preferable when access to the umbilicus is required during insertion of an umbilical catheter.

A compression-relaxation ratio with a slightly shorter compression than relaxation phase offers theoretical advantages for blood flow in the very young infant Also, compressions and ventilations should be coordinated to avoid simultaneous delivery. The chest should be permitted to fully reexpand during relaxation, but the rescuer's thumbs should not leave the chest. There should be a 3:1 ratio of compressions to ventilations with 90 compressions and 30 breaths to achieve approximately 120 events per minute to maximize ventilation at an achievable rate. Thus, each event will be allotted approximately second, with exhalation occurring during the first compression after each ventilation.

Respirations, heart rate, and color should be reassessed about every 30 seconds, and coordinated chest compressions and ventilations should continue until the spontaneous heart rate is 60 bpm.

MEDICATIONS

Drugs are rarely indicated in resuscitation of the newly born infant. Bradycardia in the newborn infant is usually the result of inadequate lung inflation or profound hypoxemia, and establishing adequate ventilation is the most important step to correct it. But if the heart rate remains <60 bpm despite adequate ventilation with 100% oxygen and chest compressions, administration of epinephrine or volume expansion, or both, may be indicated. Rarely, buffers, a narcotic antagonist, or vasopressors may be useful after resuscitation.

Route and Dose of Epinephrine Administration

Given the lack of data on endotracheal epinephrine, the IV route should be used as soon as venous access is established. The recommended IV dose is 0.01 to

0.03 mg/kg per dose. Higher IV doses are not recommended because animal and pediatric studies show exaggerated hypertension, decreased myocardial function, and worse neurologic function after administration of IV doses in the range of 0.1 mg/kg. If the endotracheal route is used, doses of 0.01 or 0.03 mg/kg will likely be ineffective. Therefore, IV administration of 0.01 to 0.03 mg/kg per dose is the preferred route. While access is being obtained, administration of a higher dose (up to 0.1 mg/kg) through the endotracheal tube may be considered, but the safety and efficacy of this practice have not been evaluated. The concentration of epinephrine for either route should be 1:10 000 (0.1 mg/mL).

Volume Expansion

Consider volume expansion when blood loss is suspected or the infant appears to be in shock (pale skin, poor perfusion, weak pulse) and has not responded adequately to other resuscitative measures. An isotonic crystalloid rather than albumin is the solution of choice for volume expansion in the delivery room. The recommended dose is 10 mL/kg, which may need to be repeated. When resuscitating premature infants, care should be taken to avoid giving volume expanders too rapidly, because rapid infusions of large volumes have been associated with intraventricular hemorrhage.

Naloxone

If administration of naloxone (dose is 0.1 mg/kg) is considered, heart rate and color must first be restored by supporting ventilation. The preferred route is IV or intramuscular. There is insufficient data to recommend endotracheal administration of naloxone in neonates. Naloxone given to a baby born to an opioid-addicted mother has been associated with seizures. Therefore, naloxone should be avoided in babies whose mothers are suspected of having had long-term exposure to opioids. Naloxone may have a shorter half-life than the original maternal opioid; therefore the neonate should be monitored closely for recurrent apnea or hypoventilation, and subsequent doses of naloxone may be required.

POSTRESUSCITATION CARE

Babies who require resuscitation are at risk for deterioration after their vital signs have returned to normal. Once adequate ventilation and circulation have been established, the infant should be maintained in or transferred to an environment in which close monitoring and anticipatory care can be provided.

Glucose

Low blood glucose has been associated with adverse neurologic outcome in a neonatal animal model of asphyxia and resuscitation. Infants who require significant resuscitation should be monitored and treated to maintain glucose in the normal range.

Induced Hypothermia and Avoidance of Hyperthermia

There is insufficient data to recommend routine use of modest systemic or selective cerebral hypothermia (e.g. 33°C to 34.5°C [91.4°F to 94.1°F]) after resuscitation of infants with suspected asphyxia. Further clinical trials are needed to determine which infants benefit most and which method of cooling is most effective. Avoidance of hyperthermia (elevated body temperature) is particularly important in babies who may have had a hypoxic-ischemic event.

WITHHOLDING AND DISCONTINUING RESUSCITATION

Morbidity and mortality for newborns varies according to region and availability of resources. Social science studies indicate that parents desire a larger role in decisions to initiate resuscitation and continue life support of severely compromised newborns. Opinions among neonatal providers vary widely regarding the benefits and disadvantages of aggressive therapies in such newborns.

Withholding Resuscitation

It is possible to identify conditions associated with high mortality and poor outcome in which withholding resuscitative efforts may be considered reasonable, particularly when there has been the opportunity for parental agreement. The following guidelines must be interpreted according to current regional outcomes:

When gestation, birth weight, or congenital anomalies are associated with almost certain early death and when unacceptably high morbidity is likely among the rare survivors, resuscitation is not indicated. Examples may include extreme prematurity (gestational age <23 weeks or birth weight <400 g), anencephaly, and chromosomal abnormalities incompatible with life, such as trisomy 13.

In conditions associated with a high rate of survival and acceptable morbidity, resuscitation is nearly always indicated. This will generally include babies with gestational age 25 weeks (unless there is evidence of fetal compromise such as intrauterine infection or hypoxia-ischemia) and those with most congenital malformations.

In conditions associated with uncertain prognosis in which survival is borderline, the morbidity rate is relatively high, and the anticipated burden to the child is high, parental desires concerning initiation of resuscitation should be supported.

Discontinuing Resuscitative Efforts

Infants without signs of life (no heart beat and no respiratory effort) after 10 minutes of resuscitation show either a high mortality or severe neurodevelopmental deficit. After 10 minutes of continuous and adequate resuscitative efforts, discontinuation of resuscitation may be justified if there are no signs of life.

"Adapted from American Heart Association, American Academy of Pediatrics. 2005 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care (ECC) of Pediatric and Neonatal Patients: Neonatal Resuscitation Guidelines. Pediatrics;2006:117. e1005- e1038."

APPENDIX

Highlights of the 2005 AmericanHeart Association Guidelines for CPR and emergency cardiovascular care BASIC LIFE SUPPORT(BLS)

A. HEALTH CARE PROVIDER (HCP)

Child CPR (1year to puberty)

1. Activate

Phone first
CPR first (after 2 minutes/5cycles)

2. Airway

Opening the Airway in trauma victim (If a jaw thrust without head extension does not open the airway, use head tilt chin lift)

3. Breathing

Check for adequate breathing in adults and presence and absence of breathing in infant/child.(Advanced HCP will assess for adequate breathing in all victims and should support oxygenation and ventilation)

Give 2 effective breaths for infant/child that causes visible chest rise. (Try couple of times to deliver effective breaths. Don't try indefinitely)

Deliver each breath over 1 second. Take a normal breath(not deep breath) (avoid excessive ventilations that are too large or too forceful; Compress a 1 L bag about halfway and a 2 L bag by one third)

Rescue breathing without compression (10 to 12 breaths/min for adults and 12 to 20 breaths/min for infant and child)

4. Circulation

Check for pulse and signs of circulation

Chest compression if HR is <60 in infant or child with signs of poor systemic perfusion

30:2 ratio of compression to ventilation(for all ages 1-rescuer CPR except newborn and 2 rescuer CPR for adults.In 2-rescuer CPR for Infant and Children use 15:2 ratio.

Use 1 or 2 hands to give chest compression for child and press on sternum at nipple line. For infants, press on the sternum just below the nipple

2 thumb encircling hands technique for 2-rescuer infant CPR should include a thoracic squeeze with fingers and forcefully compressing the sternum. Effective chest compression (Push hard- Push fast -Allow recoil-Minimal interruptions)

2-rescuer CPR with advanced airway in place, rescuers no longer provide cycle of compression with pause for ventilation

2nd Rescuer should rotate compression role every 2 minutes or 5 cycles (switch in 5 sec)

5. Foreign Body Airway Obstruction

Ask only 1 question. Are you choking? (Act if severe airway obstruction signs)

In unresponsive victim every time airway is opened, look in mouth and remove object. No tongue jaw lift and blind finger sweep.

B. LAY RESCUER

CPR first (after 2min/5 cycles)

No Jaw Thrust in Trauma Victim (use head tilt chin lift to open airway)

Check for adequate breathing in adults and presence and absence of breathing in infant/child. (take 5-10seconds but no more than 10 seconds)

Give 2 effective breaths for Infant/Child that causes visible chest rise. (If no chest rise with first rescue breath perform another head tilt-chin lift to deliver the 2nd rescue breath)

Deliver each breath over 1 second

Take a normal breath (not deep breath) (avoid excessive ventilations that are too large or too forceful)

NO RESCUE BREATHING WITHOUT CHEST COMPRESSIONS

NO CHECK FOR PULSE AND SIGNS OF CIRCULATION (after giving 2 breaths immediately begin cycle of 30 chest compressions)

30:2 Ratio of Compression to Ventilation (for all ages except newborn)

Use 1 or 2 hands to give chest compression for child and press on sternum at nipple line. For infants, press on the sternum just below the nipple line.

EFFECTIVE CHEST COMPRESSION (Push hard- Push fast -Allow recoil-Minimal interruptions)

FOREIGN BODY OBSTRUCTION

Ask only one question Are you choking? (refer to signs of mild versus severe obstruction. Act if severe airway obstruction signs: poor air exchange and increased breathing difficulty, a silent cough, cyanosis or inability to speak or breathe)

MAJOR BLS CHANGES FOR ALL RESCUERS

1. Emphasis of effective chest compressions, push hard and fast (100/min). Allow chest to recoil completely. Minimal interruptions in chest compressions
2. One universal (30:2) Compression to ventilation ratio for all lone rescuers
3. Recommendations for 1-second Breaths. Don't give too many-too large-too forceful breaths
4. Attempted defibrillation: 1 shock, then immediate CPR. Check rhythm after giving about 5 cycles (2 min)
5. Reaffirmation of 2003 ILCOR statement:AEDs recommended for children >1 Yr.

MAJOR PALS CHANGES

Use of advanced airways
Verify correct tube placement with clinical exam and device (use a colorimetric detector or capnography)
Cuffed ETT in children can be used : formula Age in years/ 4+3
LMA can be used when ET intubation not possible
CPR with advanced airway: Compression without pause for ventilation
Vascular preffered to endotracheal drug administration
Routine use of high dose epinephrine not recommended
Standard dose 0.01 mg/kg IV/IO should be used
Timing of drug administration during pulseless arrest
CPR—1 SHOCK—CPR (5 cycles or 2 minutes). Give drug during CPR. Drug delivery should not interrupt CPR. Rhythm check after 5 cycles

RHYTHM DISTURBANCES AND DEFIBRILLATION

Deemphasize lidocaine for VT VF compared to amiodarone

Give lidocaine only if amiodarone unavailable.

changes in timing of drug administration in treating pulseless arrest, the use of 1 shock followed immediately by CPR.

The algorhithm for treatment of tachycardia with adequate perfusion is not indicated

The superiority and greater safety of biphasic over monophasic shocks for defibrillation

POSTRESUSCITATION CARE

Hypothermia: Possible benefit of induced hypothermia for 12 to 24 hours for patients who remain comatose after resuscitation from cardiac arrest
Role of INODILATORS to treat post resuscitation myocardial depression.
Termination of resuscitative efforts:Intact survival has been reported following prolonged resuscitation and absence of spontaneous circulation despite 2 doses of epinephrine.

NEONATAL RESUSCITATION

Room air or oxygen concentration of less than 100% oxygen can be used for resuscitation.

Routine intrapartum oropharyngeal and nasopharyngeal suctioning is no longer recommended in meconium staining.

Devices for assisting ventilation that can be used are self inflating bag, a flow inflating bag, or a T piece. LMA can also be used in special cases.

Indications of ventilation and confirmation of ETT placement by exhaled CO_2 is recommended as the primary technique.

Drug therapy: Higher dose IV Epinephrine is not recommended. Naloxone is not recommended during the primary steps of resuscitation and through ETT.

Temperature control: Polyethylene bags may help maintain temperature of VLBW babies.Avoid hyperthermia.

Witholding Therapy: Resuscitation is not indicated in certain conditions of early death and unacceptable high morbidity (examples gestation <23 wks, birth weight <400 g, Anencephaly, Trisomy 13). Resuscitation is always indicated in conditions with a high rate of survival and acceptable morbidity. Parental desires of initiation of resuscitation in uncertain prognosis in which survival is borderline, the morbidity rate is relatively high and the anticipated burden to the child is high.

Withdrawing therapy: Infants without signs of life after 10 min of continuous and adequate resuscitative efforts

CHAPTER 4

Airway Management

Praveen Khilnani, Dhiren Gupta, Guiseppe Marraro

Pediatric airway management essentially involves a good working knowledge of differences in pediatric and adult airway.

Anatomical Differences

Fetal larynx is at (cervical vertebra level) Cl, C2 and C4. In the infant, larynx is located opposite C3 to C4. Arytenoids are relatively large. Epiglottis remains at a 45 degree angle to the anterior pharyngeal wall and is omega shaped. It is tubular with a narrow base and long. Infant larynx is funnel shaped (Fig. 4.1). The narrowest portion of the infant airway is the area of cricoid ring. The vocal cords are concave and at an angle to the trachea. The trachea is approximately 5 to 7 cm long at birth. The main bronchi branch from the trachea at approximately equal angles, but as the patient grows, the right main stem bronchus is more in line with the trachea. At four to six months of age, the epiglottis loses contact with the soft palate, and the infant is able to breath by mouth. By 12 years of age, the epiglottis and the larynx are in the adult location of C6. The narrowest portion of the adult airway is the glottic opening. A large epiglottis constantly touching the soft palate prevents mouth breathing. By 4-5 months of age as the larynx descends down, epiglottis no longer touches the soft palate thereby allowing mouth breathing. The child's tongue is relatively large for the smaller oral cavity due to buccal fat pads and receded mandible. Increase in size of the tongue (e.g. hemangioma, Down's syndrome, Beckwith Wiederman syndrome) or markedly receded mandible (Pierre Robin, Treacher Collins syndrome) readily leads to airway obstruction.

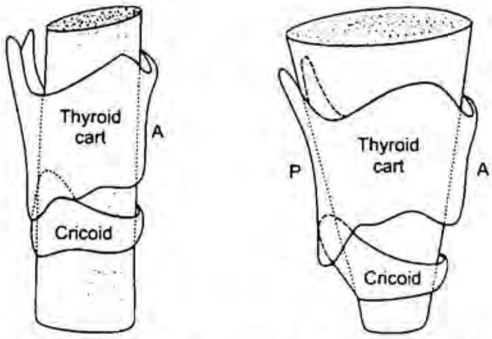


Fig. 4.1: Adult airway(left) and pediatric airway(right)

In the child, the attachment of the vocal cords is lower at its anterior attachment than posteriorly. In the adult, the vocal are on a horizontal plane occasionally making endotracheal intubation more difficult in the infant as a result of the tube being held up at the anterior commissures of the vocal folds.

The relatively narrow subglottic area is predisposed to edema from croup or following endotracheal intubation or bronchoscopy. Swelling in this area in the child may cause stridor and respiratory distress. An equivalent amount of swelling in the adult would have minimal effects due to much larger diameter, resistance being inversely proportional to the radius of the lumen of the airway.

Physiological Differences

In the neonate, the nasal passages account for 25 percent of the total resistance to airflow compared to 60 percent in the adult. Lower airway contributes majority of airway resistance due to relatively small size of the airways and lack of supportive structures. Due to relatively soft-cartilagenous support, the larynx, trachea and bronchi in the infant are considerably more compliant than in the adult. Various distending and compressive forces have a significant effect on airway caliber. The extrathoracic trachea is subject to different stresses than the intra-thoracic trachea. With normal inspiration, the negative pressure developed within the chest is transmitted to the large airways including the intrathoracic trachea tending to cause dilation. However, at the thoracic inlet, dynamic compression occurs as a result of the pressure difference between atmospheric pressure and the negative pressure within the extrathoracic trachea. With normal inspiration, this compression is relatively slight and patency of the airway is not compromised. Normal expiration is a passive process driven by the elastic recoil of the lung. Transmural pressures are positive along the entire tracheobronchial tree. There are no significant changes in airway caliber. With obstruction of the extrathoracic airway (e.g. laryngotracheobronchitis, supraglottitis, foreign body), inspiratory effort leads to increased negative pressure within the chest and airway. This leads to a greater difference between ambient pressure and the negative pressure within the extrathoracic trachea. As a result, significant dynamic inspiratory collapse of the extrathoracic trachea will occur, particularly at the thoracic inlet. Intrathoracic airway caliber is only minimally affected because inspiratory pressures within the airways and pleural pressure fall to a similar extent.

The phenomenon of dynamic collapse of the airway has particular relevance in treating acute airway obstruction. Marked transmural pressure changes occur when the infant is agitated and crying. Thus efforts to relieve anxiety and crying are crucial in minimizing dynamic collapse of the airway. In addition, applying continuous positive pressure via a face mask and adjustable pop off valve in the severely obstructed child will counteract dynamic collapses of the airway and facilitate gas exchange.

In summary, Upper airway in children is cephalad, funnel shaped with narrowest area being subglottic (at the level of cricoid ring), as compared to adults where the upper airway is tubular with narrowest part at the vocal cords. Airway resistance increases inversely by 4th power of radius; i.e. in an already small airway even one mm of edema or secretions will increase the airway resistance and turbulent flow markedly necessitating treatment of airway edema, suctioning of secretions, measures to control secretions.Dynamic airway collapse is common. keeping in mind the differences in airways, following discussion involves the common airway management techniques in pediatric age group.

AIRWAY MANAGEMENT TECHNIQUES

Simple maneuvers allow the patency of airway, such as correct positioning of the neck and the head **(Chin lift, head tilt and jaw thrust, see Figs 2.3 and 2.4 in chapter 2)**, and clearing the mouth of blood, secretions, broken teeth and debris. Lateral decubitus position helps with ventilation and spontaneous elimination of sectretions from the mouth. It is advisable in all comatose patients, in patients with insufficient muscle tone of the neck and during awakening from narcosis. Simple maneuvers such as jaw thrust, head tilt and chin lift can favour patency of airway alone or in combination with lateral decubitus positioning.

Head- tilt maneuver can be attempted by extending the neck and pulling the mandible forward, thereby lifting the tongue from the posterior pharyngeal wall. This technique helps to prevent airway obstruction by the tongue and will result in a patent airway. Hyperextension of the neck must be avoided in small infants since it may lead to compression of the soft tracheal cartilage.

Chin lift and Jaw-thrust maneuver can be attempted with the patient in any position by placing two or three fingers at each angle of the jaw and then lifting the chin and jaw forward. It is generally accompanied by head tilt maneuver and helps with the maintenance of patency of the airway and stimulates ventilation. If cervical trauma is suspected, jaw thrust should be applied preferably without head tilt to avoid spinal dislocation or further injury. However jaw thrust is difficult to administer, so for lay rescuers out in the field, head tilt and chin lift to open airway even in trauma victim has been added to the 2005 recommendations by american heart association. As a word of caution Jaw thrust maneuver could lead dislocation of the jaw, especially in cases of congenital malformation and can be difficult to apply effectively in cases of trismus.

Oral and Nasal Devices

Non invasive oral and nasal airways can restore and maintain airway patency and facilitate the passage of gases into the pharynx and the larynx.

Oral airways are useful in cases of non patency of nostril and choane, in the presence of macroglossia, hypotonic muscle of chin triangle and of neck, and when the mouth is difficult to maintain adequately open. The presence of an oral airway can stimulate vomiting if an incorrect caliber is used and worsen respiratory insufficiency (Figures 4.2A to C). During manual ventilation it can favour the passage of gases into the stomach. Its use is indicated during spontaneous or assisted ventilation by mask and requires deep anesthesia to abolish tongue reflexes. Its shape (central lumen) allows easier bronchial suctioning.

Recently, a new oral airway suitable for adolescent and young adults, **COPA (Cuffed Oro-Pharyngeal Airway)** has been clinically evaluated. The method of insertion of this device is the same that of a standard oral airway. After proper insertion has been achieved, the balloon is then inflated so as to ensure a close fit to oropharyngeal structures.

Nasal/nasopharyngeal airways may be useful in cases of impossible access through the mouth because of anomalies of maxillofacial structures, tumors and head trauma, and when pharyngeal CPAP must be applied avoiding tracheal intubation.

A nasal tube positioned with the tip in the posterior pharynx can be utilized. A larger diameter tube than that used in tracheal intubation is sufficient. Proper length may be estimated as distance from nares to angle of mandible (Figs 4.3 and 4.4). Lower tube placement stimulates coughing and vomiting and may lead to the passage of gases into the esophagus.

Tube insertion must not provoke trauma to nasal cavity (e.g. bleeding from hypertrophied adenoids or nasal turbinate injury). In cases of facial trauma with problematic patency of nares and choanae, nasopharyngeal airway should be avoided. Naso-

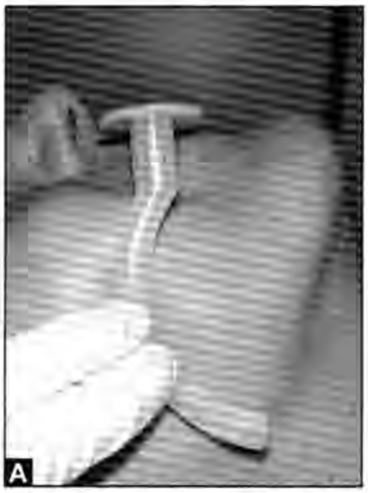


Fig. 4.2A: Correct estimation of size of oral airway (mouth to angle of mandible) *(For color version see Plate 1)*

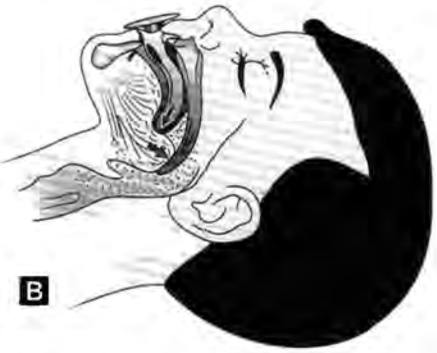


Fig. 4.2B: Too small oral airway

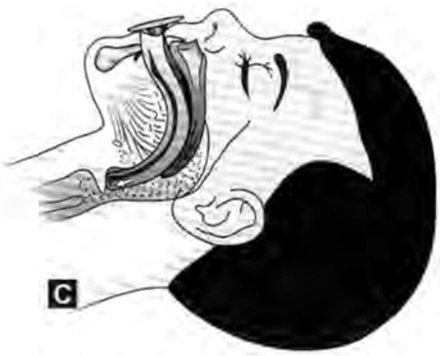


Fig. 4.2C: Too large oral airway

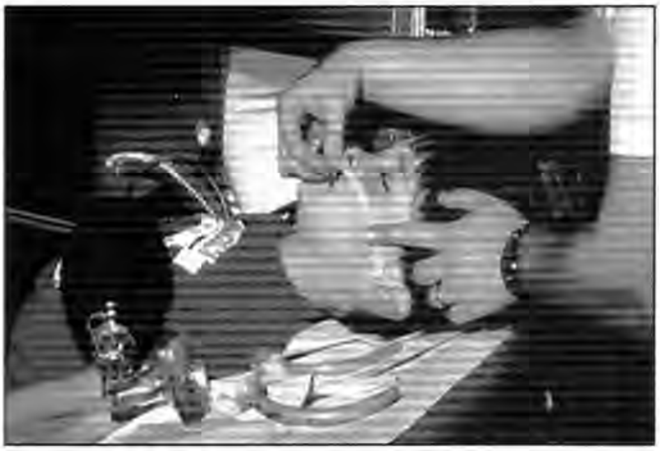


Fig. 4.3: Proper placement of NP airway *(For color version see Plate 1)*

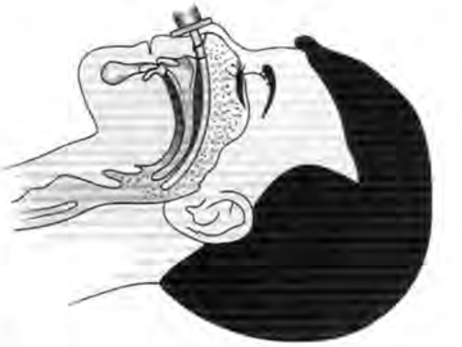


Fig. 4.4: Nasopharyngeal (NP) airway: Estimation of correct size of nares to angle of mandible

tracheal tubes have been reported to be accidentally placed inside the base of skull via a skull fracture.

Laryngeal Mask Airway (LMA)

This is a recently introduced technique of securing airway by relatively inexperienced medical personnel such as nurses and paramedics, who may not succeed in placing an endotracheal tube in a pediatric patient. The main principle behind its use is to place the tip of LMA in the beginning of the upper esophagus to occlude it, so that the portion of LMA superior to the upper end of esophagus outlines the glottis thereby placing a mask on the larynx (laryngeal mask airway) (Fig. 4.5). It can be used to maintain airway, provide bag ventilation, used for passage of a flexible bronchoscope as well as passing a suction catheter for suction of copious secretions. The laryngeal mask, allows maintenance of airway patency but does not resolve all ventilatory problems in children. The use in neonate and infant has to be cautious and more clinical experience needs to be acquired before widespread use can be recommended. The LMA should not be used as a substitute when endotracheal intubation is necessary.

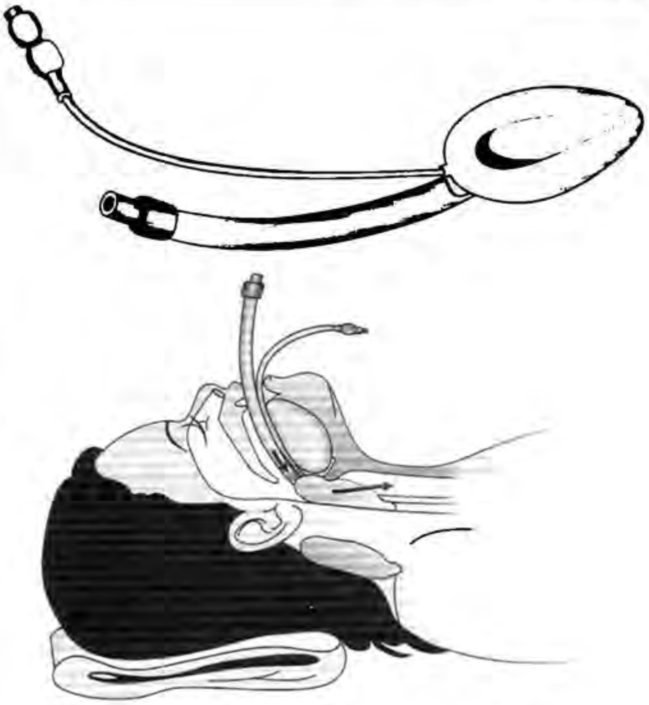


Fig. 4.5: Laryngeal mask airway in place

Many children with severe facial malformations that make tracheal intubation hazardous, or even impossible, greatly benefit from its use, since a tracheal tube can be introduced through the tube and advanced blindy into the trachea. This technique has led the manufacturer to develop a variant of the laryngeal mask (Fastrach) designed to allow insertion of a tracheal tube through the laryngeal mask, the mask is removed and the tracheal tube is then connected to ventilatory bag.

Benefits are avoiding tracheal intubation, fiberoptic tracheal intubation and reduced hemodynamic variations compared to tracheal intubation

Disadvantages are difficult insertion and easy displacement, partial or complete airway obstruction, laryngospasm in cases of insufficient sedation and anesthesia, uvular, pharyngeal and laryngeal trauma.

The laryngeal mask is not indicated in the presence of vomiting, regurgitation and full stomach, in emergency, in chronic lung disease and in patients with large quantities of secretions, in hypertrophic tonsils, in patients with malformation of oral cavity. Various adult and pediatric sizes are available (Table 4.1). It is contraindicated in patients with full stomach and in patients requiring intubation due to airway obstruction due to inflammation or edema.

Bag Mask Ventilation

This is one technique that every health care provider needs to be familiar with. Self infating bag(Ambu) or anesthesia bag (Mapleson/C-Circuit, made by Intersurgical, Vital sign)can be used with a proper sized mask attachment as well as fresh gas source for oxygen (central or via a gas cylinder). With maintaining the proper seal around the mouth and the nose of the child (Figure C around mouth made by forefinger and thumb holding the mask, and figure E with three fingers at the mandible firmly holding the jaw in mid extension position, all with one hand and the other hand is used to squeeze the bag. Alternatively two hands can firmly hold the mask, over the face maintaining a tight seal around the mouth and the nose, and an assistant can squeeze the bag to deliver the breaths (Fig. 4.6). Hyperextension at the neck should be avoided in small infants as it can lead to tracheal collapse. Another precaution that should be taken in small infants includes avoiding too much pressure on the anterior part of the neck while holding the jaw, as this can cause airway obstruction.

Table 4.1: LMA size patient selection information

Max.	Inflation volume (ml)	
LMA-ClassicTM		
1	Neonates/Infants up to 5 kg	4
1½	Infants 5-10 kg	7
2	Infants/Children 10-20 kg	10
2½	Children 20-30 kg	14
3	Children 30-50 kg	20
4	Adult 50-70 kg	30
5	Adult 70-100 kg	40
6	Large Adult over 100 kg	50
LMA-FlexibleTM		
1	Neonates/Infants up to 5 kg	4
1½	Infants 5-10 kg	7
2	Infants/Children 10-20 kg	10
2½	Children 20-30 kg	14
3	Children 30-50 kg	20
4	Adult 50-70 kg	30
5	Adult 70-100 kg	40
6	Large Adult over 100 kg	50
LMA-UniqueTM		
3	Children 30-50 kg	20
4	Adult 50-70 kg	30
5	Adult 70-100 kg	40

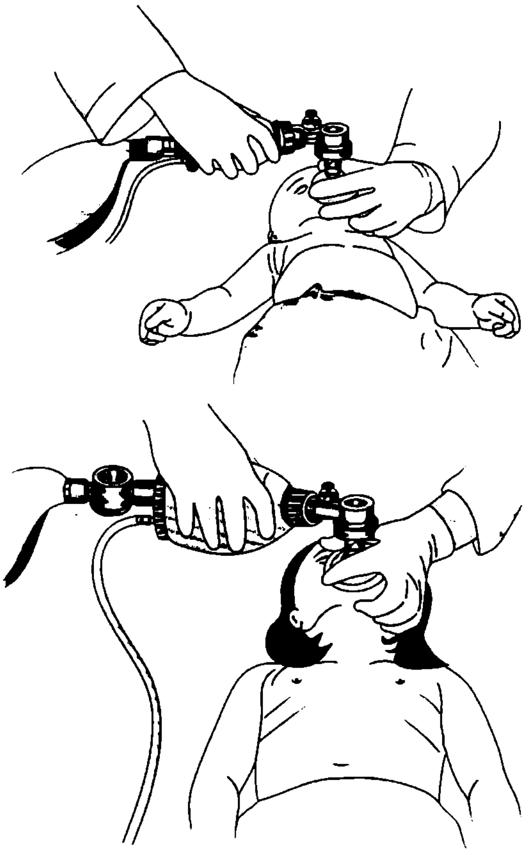


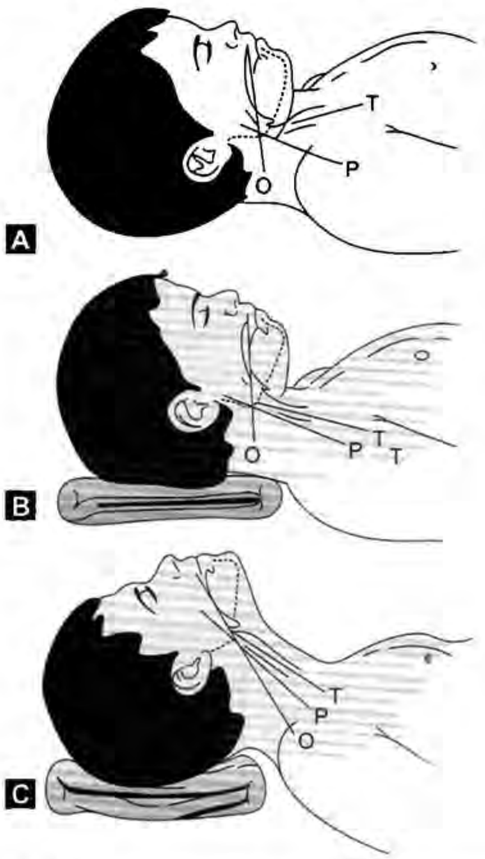
Fig. 4.6: Technique of bag mask ventilation

Endotracheal Intubation

Main indications for endotracheal intubation are: (i) upper airway obstruction; (ii) respiratory failure requiring assisted ventilation; (iii) cardiopulmonary resuscitation; and (iv) administration of general anesthesia.

Elective Oral Endotracheal Intubation

For successful intubation, position of the patient with respect to the person performing the intubation is extremely important. As shown in Figs 4.7A to C, alignment of oral, pharyngeal and tracheal axes is important for good visualization of glottic area.



Figs 4.7A to C: C is the Ideal Patient position for laryngoscopy and endotracheal intubation when oral (O), pharyngeal (P) and tracheal (T) axis are aligned

Ideal position for endotracheal intubation is the sniffing position with flexion at the neck and extension at the atlanto-occipital joint. Oxygen supply, suction and appropriate pediatric size bag, mask, airways, stylets, endotracheal tubes and suction catheters should be readily available (Figure 4.8). A short acting muscle relaxant (succinylcholine 2 mg/kg IV) is commonly used to facilitate endotracheal intubation. Intravenous atracurium (short acting non-depolarizing muscle relaxant) can be used if succinyl choline is contraindicated, such as in patients with crush injury, renal failure, myopathy, burns, increased intra-cranial pressure, history of malignant hyperpyrexia or familial pseudocholinesterase deficiency. Choice of a sedative varies from intravenous diazepam, midazolam or morphine to intravenous pentothal sodium, propofol or ketamine. Midazolam and diazepam are easily available and practical. After proper sedation and muscle relaxation has been achieved, the patient should receive bag mask ventilation with 100% O_2 for 2-3 minutes. The purpose is to wash out nitrogen from the lungs thereby minimizing chances of hypoxemia during the apnea, while endotracheal intubation is being performed.

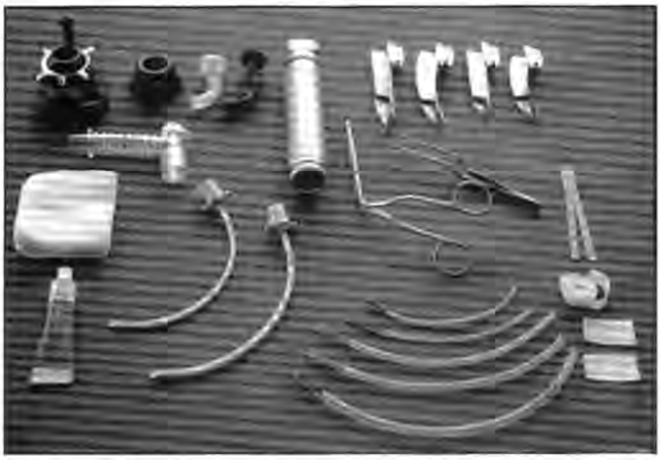


Fig. 4.8: At a glance view of intubating insert equipment

The mouth is opened with thumb and forefinger of the right hand. Laryngoscope blade is introduced near the right angle of the mouth by the left hand between the tongue and the soft palate. Under direct vision, the tip of the blade is passed along the tongue until the epiglottis is visualized. A straight blade is commonly used for neonates, infants and for children under two years of age (Fig. 4.9). In older children curved laryngoscope blade(macintosh blade) can be used (Fig. 4.10). Choice of blade used should not be a rule, rather, it should depend upon the comfor level of the person performing the procedure.

For better visualization of vocal cords, the tongue may be pushed to the left by laryngoscope blade The epiglottis is lifted to uncover the glottic opening and vocal cords. Sometimes an assistant's finger used to push at the level of cricoid cartilage makes visualization of the glottic opening easier. Suction of oral secretions may also help the visualization o the glottic opening better. Endotracheal tube(ETT (with or without stylet) should now be passed beyond the vocal cords.

Size of the endotracheal tube(in mm) can be estimated by simple formula: age in year/4 +

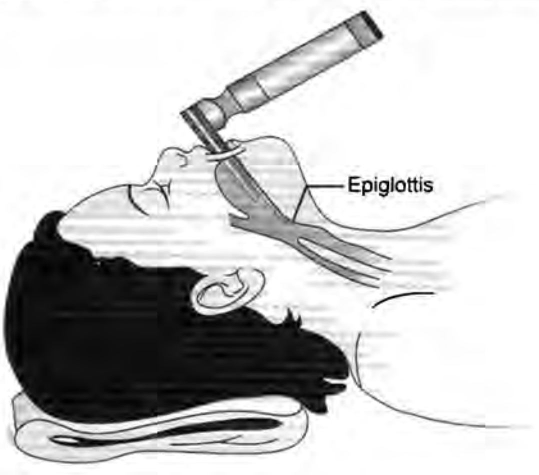


Fig. 4.9: Straight blade in place

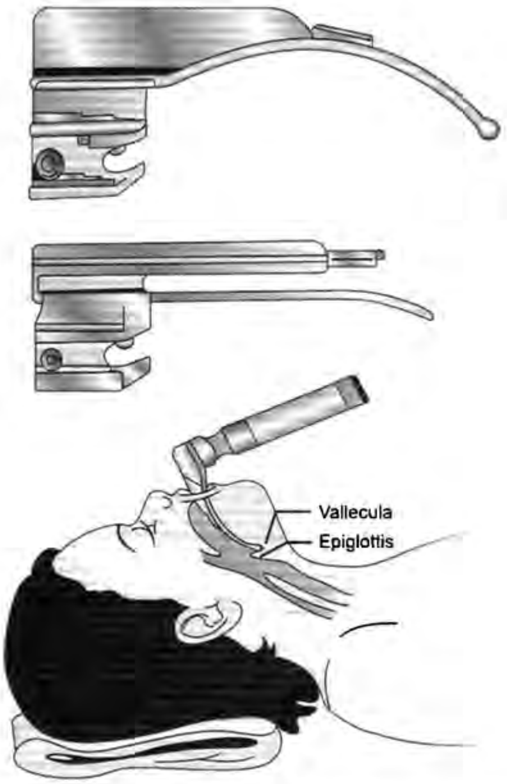


Fig. 4.10: Curved and straight laryngoscopic blades. In younger patients, neonates straight blade is preferred

(uncuffed tube) and for cuffed tube: age in years/ 4+3.

Alternatively the size equal to the width of the little finger of the patient is a rough estimate. Cuffed tube may be used if patient is older than 8 years of age , or if there is too much leak aroud the proper size endotracheal tube due to low compliance of the lungs. Various sizes of laryngoscopes and endotracheal tubes required for different age groups . In exceptional cases where lung pathology requires higher airway pressures to achieve the desired tidal volume, even 2.5 mm cuffed tubes are available.

It is important to remember that, in children, the cricoid ring is the narrowest part of the larynx. Therefore, the endotracheal tube must pass the subglottic cricoid ring after it has traversed the vocal cords before proper placement can be assured. In some patients, the endotracheal tube may pass beyond the vocal cords, but is difficult to pass further than the subglottic area at the level of the cricoid ring. In these situations, an endotracheal tube of a smaller size may be needed.

If a cuffed endotracheal tube is used, cuff should be inflated after endotracheal intubation, until there is no air leak around the cuff. Breath sounds should be checked bilaterally. Fog will usually be seen upon expiration in the endotracheal tube. Louder breath sounds on right may indicate right main-stem bronchial intubation. The endotracheal tube should be withdrawn until equal breath sounds are heard on both sides of the chest. A five point auscultation should be done, bilaterally over upper chest anteriorly, lower chest on the sides and over upper abdomen. Placement can be confirmed by the colorimetric end tidal carbon dioxide sensor after 4-5 breaths have been given. No CO_2 will be sensed in case of esophageal intubation. Proper placement should be checked by chest X-ray film. Chest radiograph will usually confirm proper placement (right mainstem intubation and esophageal intubation can occur) in most cases. ETT tip should be below the level of the clavicles and above the level of carina. The endotracheal tube should now be well secured with the tape or the endotracheal tube holder. Oral airway should also be inserted if the patient has teeth to prevent biting on the tube, especially if no muscle relaxant will be used.

Emergency Oral Endotracheal Intubation (RSI-Rapid sequence intubation) (Fig. 4.11)

The procedure for emergency endotracheal intubation is essentially similar to elective intubation,

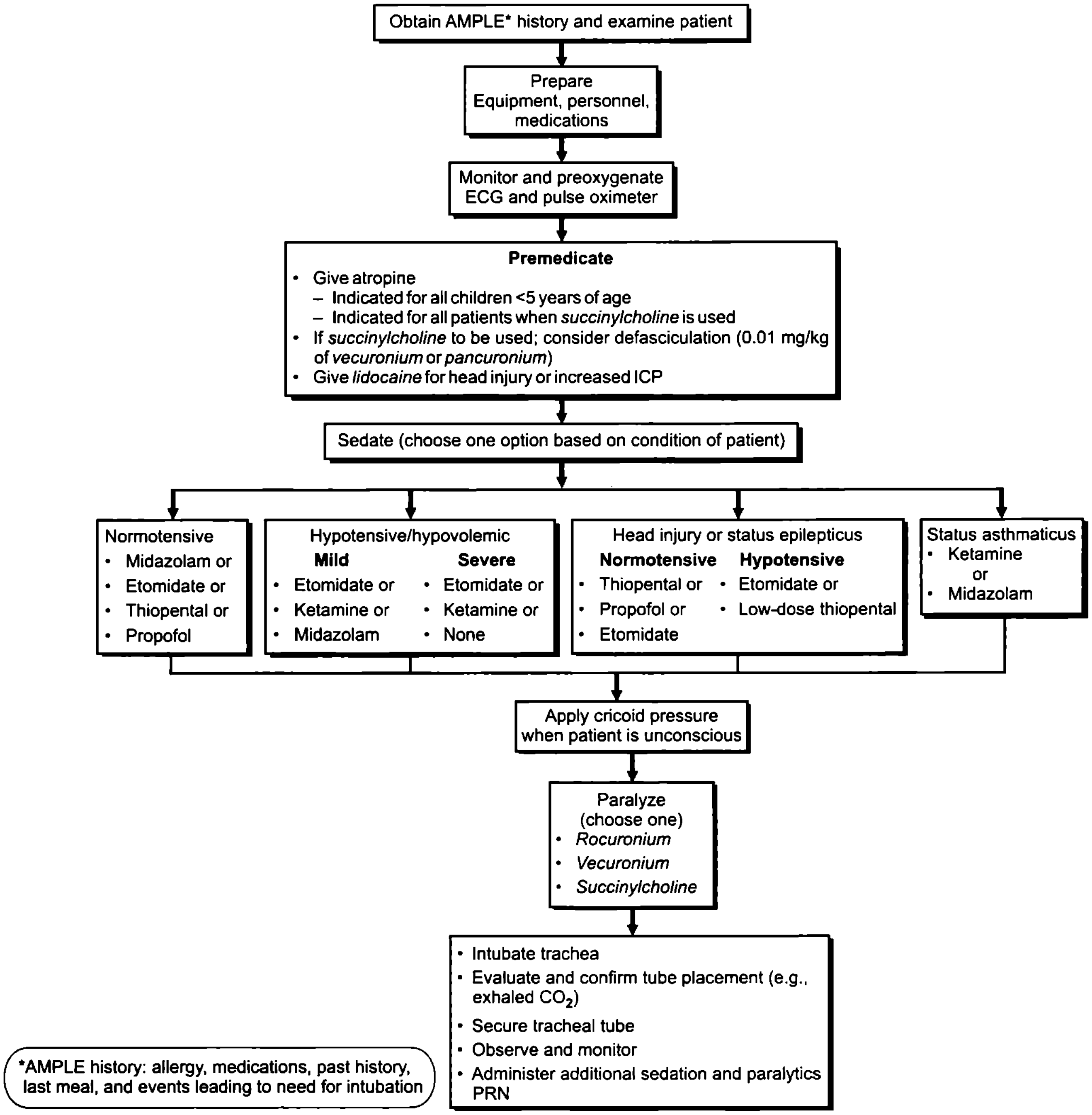

Obtain AMPLE* history and examine patient
Prepare
Equipment, personnel, medications
Monitor and preoxygenate
ECG and pulse oximeter
Premedicate
• Give atropine
– Indicated for all children <5 years of age
– Indicated for all patients when *succinylcholine* is used
• If *succinylcholine* to be used; consider defasciculation (0.01 mg/kg of *vecuronium* or *pancuronium*)
• Give *lidocaine* for head injury or increased ICP
Sedate (choose one option based on condition of patient)
Normotensive
• Midazolam or
• Etomidate or
• Thiopental or
• Propofol
Hypotensive/hypovolemic
Mild
• Etomidate or
• Ketamine or
• Midazolam
Severe
• Etomidate or
• Ketamine or
• None
Head injury or status epilepticus
Normotensive
• Thiopental or
• Propofol or
• Etomidate
Hypotensive
• Etomidate or
• Low-dose thiopental
Status asthmaticus
• Ketamine
or
• Midazolam
Apply cricoid pressure when patient is unconscious
Paralyze
(choose one)
• *Rocuronium*
• *Vecuronium*
• *Succinylcholine*
• Intubate trachea
• Evaluate and confirm tube placement (e.g., exhaled CO2)
• Secure tracheal tube
• Observe and monitor
• Administer additional sedation and paralytics PRN
*AMPLE history: allergy, medications, past history, last meal, and events leading to need for intubation

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Fig. 4.11: Algorithm for rapid sequence intubation (RSI)

except the patient is considered to have a full stomach; therefore, the procedure is modified to prevent aspiration of gastric contents into the lungs. **AMPLE is a mnemonic followed for assessment before RSI to check for allergies, medications, past history, last meal and events that led to the need of RSI.**

Atropine is given. A priming (precurarizing) dose of pancuronium or vecuronium 0.01 mg/kg intravenously is first given followed by pre-oxygenation with 100 percent oxygen for two minutes. Priming dose prevents muscle fasciculations following administration of succinyl choline to prevent an increase in intra-abdominal, and intragastric pressure

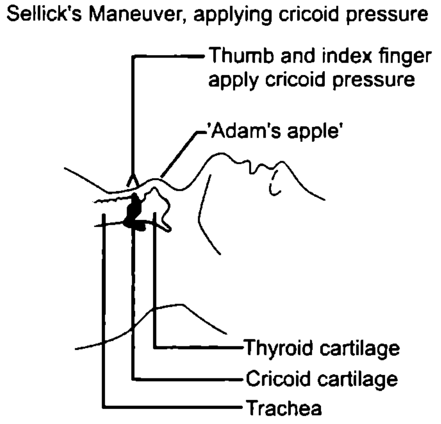

Sellick's Maneuver, applying cricoid pressure
Thumb and index finger apply cricoid pressure
'Adam's apple'
Thyroid cartilage
Cricoid cartilage
Trachea

Fig. 4.12: Sellick's maneuver (application of cricoid pressure)

Ketamine, midazolam, propofol or a short acting barbiturate (midazolam is practical) may now be given followed by pressure on the cricoid cartilage (Sellick's maneuver: Fig. 4.12) applied by the assistant. Etomidate, a short acting intravenous induction agent has recently gone out of favour due to reported hypotension. Sellick maneuver occludes the upper end of the esophagus, which is compressed between the cricoid cartilage and the cervical vertebra, thereby preventing a passive regurgitation and aspiration of the stomach contents.

Succinylcholine/atracurium may now be given. Bag and mask ventilation is avoided to prevent stomach distention and possible regurgitation. Endotracheal intubation is performed after the patient's jaw is felt adequately relaxed. With the recent availability of short acting nondepolarizing muscle relaxants (i.e. Atracurium, rocuronium), the use of succinylcholine may decline in the future. However, currently succinyl choline (a depolarizing muscle relaxant) remains the muscle relaxant of choice in most situations. Contraindications include, raised intraocular pressure, renal failure, hyperkalemia, raised intracranial pressure, history of malignant hyperthermia, crush injuries and various myopathies. Fasciculations induced by succinylcholine cause a release of potassium from the myocytes resulting in dysrhythmias deteriorating to ventricular fibrillation and cardiac arrest.

Nasotracheal Intubation

Some physicians prefer nasotracheal intubation when long-term ventilation is required. It is relatively easy to keep nasal tube well secured as compared to oral endotracheal tube. Main disadvantage of long-term nasal intubation is chronic sinusites caused by obstruction of the ostia draining nasal sinuses. Nasotracheal intubation is performed electively via one of the nostrils. After proper lubrication endotracheal tube is passed via the nostril, until it is visualized in the pharynx by oral laryngoscopy. If one nostril does not allow passage, usually other nostril will allow passage of the endotracheal tube. Force should not be used in inserting the tube as this may result in severe bleeding from the nasal turbinates. Once visualized tip of the tube is guided towards the vocal cords by grasping the tube with Magill's forceps in the pharyngeal cavity, and the endotracheal tube is pushed further in the trachea. Nasotracheal intubation is contraindicated in patients with basilar skull fracture, maxillofacial trauma and coagulopathies.

DIFFICULT INTUBATION

Difficult intubation is a frequent and frustrating problem for the doctors, in pediatric age. *Technical inability to perform intubation is the most frequent cause, mostly due to improper positioning and poor visualization of the vocal cords.* Severe brain damage and death can follow failed intubation and consequent hypoxia in more than 70 percent of cases.

Difficulty in intubation can occur during the elective procedure or most frequently in emergency. It can be suspected or unexpected and can be due to a difficult visualization of glottis or difficult positioning of the tube in trachea. In some cases difficult intubation could be related to improper diameter of the tube and/or the size of laryngoscope.

Newborns and infants present an increase of oxygen consumption and a reduced oxygen reserve. For these reasons hypoxia occurs rapidly when ventilation is inadequate.

In the newborn and in the infant the neck is short, the tongue is large and occupying the mouth, larynx is situated at level of second cervical vertebra (until 5 years), vocal chords are higher and anteriorly positioned, and epiglottis is longer and angled. Airway diameters are small in children under 6 years and alveoli are growing. Newborns and premature babies in particular have a relatively low functional residual capacity. Children under 3 years have the tendency for early airway closure or collapse and subsequent gas trapping.

Hyperextention of the neck does not allow better visualization of laryngeal glottis as in adults. Mid flexion/sniffing position is advisable to prevent airway collapse induced by hyperextension of the neck.

As mentioned earlier, difficult intubation can be suspected or unexpected, but one should be prepared for such a situation. In some cases, difficult intubation could be related tube size, use of stylet and/or the size of laryngoscope. Mostly it is due to improper positioning of the patient or the operator leading to difficulty in visualization of laryngeal structures.

In case of suspected difficult intubation a well-planned approach is necessary. Well-trained specialist (pediatric intensivist or anesthesiologist) should be present. Reduced complications and failures in intubation have been reported in well-planned situations. Accurate preprocedure assessment and clinical examination can reduce the difficulty in performing intubation.

Several methods have been suggested in cases of difficult intubation. Familiarity with these methods must be acquired in children with normal anatomy before managing children with abnormal airway. In cases of suspected or unexpected difficult intubation, spontaneous ventilation should always be maintained. Neuromuscular blockade administered to facilitate intubation can result in total airway obstruction with consequent impossibility to perform manual ventilation, because the muscle tone of the tongue, cervical and laryngeal muscles, and suspensory ligaments is lost. Moreover, the loss of spontaneous breathing sounds eliminates a guide to locating the laryngeal inlet.

Difficult intubation can be seen in two major groups of patients:

- In the first group the visualization of larynx is easy under direct laryngoscopy but a supraglottic, glottic or subglottic stenotic lesion prevents passage of the usual size tube
- In the second group direct visualization of the glottis is difficult or impossible because of facial, oral congenital or acquired malformations.

The first group includes congenital malformations such as cricoid ring stenosis, webs, cysts and laryngocele, subglottic hemangiomas and acquired lesions such as epiglottitis, croup, subglottic stenosis juvenile rheumatoid arthritis, the presence of foreign bodies, external trauma, thermal and chemica trauma, and laryngeal papillomatosis.

Laryngotracheomalacia and vocal cord paresis even though present with a narrow airway, allow the passage of an endotracheal tube of usua diameter. Laryngotracheo-esophageal cleft allows an easy passage of the tube through the glottis bu the placement of the tube in trachea is difficult due to the anatomical malformation.

The second group is represented by congenita malformations characterized by micrognathia (due to mandibular hypoplasia) including the craniofacia dysmorphologies (e.g. Pierre Robin syndrome), the mandibulofacial dysostosis (Treacher Collins syndrome), the mandibulo-auriculo-oculovertebra dysplasia (Goldenhar syndrome), the oculo mandibulo dyscephaly (Hallerman-Streiff syndrome), Mobius and Cornelia de Lange syndromes.

Lip and palate clefts permit a normal passage through the glottis but laryngoscope positioning is difficult (Fig. 4.13).

MANAGEMENT OF DIFFICULT INTUBATION

1. Awake "blind intubation"
2. Direct laryngoscopy
3. Bullard laryngoscope
4. Indirect intubation:
   - Fiberoptic laryngoscopy
   - Prism devices for laryngoscopy, dental mirror
   - Lighted stylet or lightwand
5. Retrograde translaryngeal intubation
6. Transtracheal ventilation
7. Surgical access:
   - Cricothyroidotomy
   - Tracheostomy

Awake "Blind Intubation"

This technique does not require equipment and can be performed even when blood or secretions are present. The technique is especially used in dyspnoic patients because their breath sounds are easy to hear and they tend to maintain their glottis open. Once

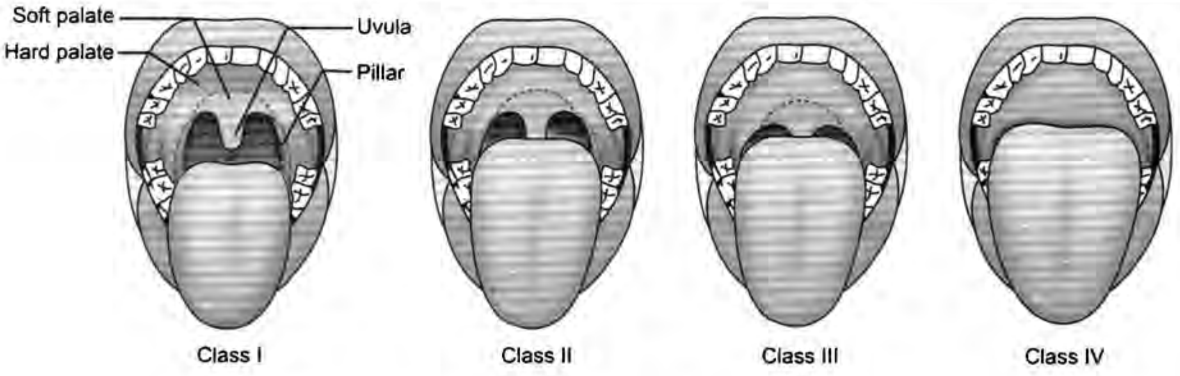


Fig. 4.13: Mallampati classification for difficult airway

the tube is in the nasopharynx, it should be directed using breath sounds as a guide. Palpation of the neck, push of larynx, 180° rotation of the tube and flexion or extention of the neck will assist in the correct positioning of the tube.

The blind technique can be used in all pediatric ages including neonates (2.5 mm tracheal tube can be applied) and may benefit from continuous end tidal CO_2 measurement to confirm the correct placement of the tube. This technique may also be of value in patients with fracture of the cervical spine or completely rigid spine (e.g. Mucopolysaccharidoses) because tracheal intubation can be performed without movement of neck.

Direct Laryngoscopy

Intubation may result difficult to perform using direct laryngoscope (due to incorrect/inadequate size, curved or straight blade) more than curved, or incorrect positioning of the head (hyperextention of the neck). In these cases, utilization of suitable material and correct positioning of the head allows the intubation.

If visualization of vocal cords is impossible, blind intubation can be performed under laryngoscopy. The tube is passed through the nose in pharynx and can be positioned under epiglottis using a pair of Magills forceps. External manipulation of larynx during laryngoscopic vision, can be helpful to facilitate intubation. The maneuver is facilitated maintaining spontaneous breathing which allows visualization of gases coming from trachea (presence of small bubble of saliva).

Bullard Laryngoscope

It is an interesting piece of equipment for glottis visualization but requires an experienced operator because the visualization is so different from that obtained by a standard laryngoscope. The positioning of the endotracheal tube can partially reduce the visualization of the laryngeal inlet during positioning with consequent difficulty in maneuver.

The Bullard Laryngoscope uses mirrors as well as fiberoptic technique. It is designed to offer visualization around a 90 degree bend at the tip in order to be helpful in patients having midfacial hypoplasia (e.g. Treacher Collins, Goldenhar syndromes) which causes an exaggeration of the acute angulation of the base of the tongue to the glottis opening. The blade is inserted into the oral cavity like a conventional laryngoscope and gently advanced to visualize the laryngeal inlet. At this point a styletted endotracheal tube with a bent tip is inserted alongside the laryngoscope blade and pushed into the trachea.

Several laryngoscope blades have been proposed for difficult intubation in specific circumstances. Belscope, an angulated laryngoscope and rigid tubular laryngoscope, can be recommended to visualize the glottis in the presence of severe edema of the laryngeal inlet or a large tongue.

Indirect Approach

- Fiberoptic Laryngoscopy
- Prism Devices or Dental Mirror
- Lighted Stylet or Lightwand

Fiberoptic Intubation (Figs 4.14 and 4.15)

The availability of increasingly smaller fiberoptic laryngo-scopes has led to their widespread use in pediatrics, facilitating most notably difficult intubation and diagnostic bronchoscopy.

Fiberoptic bronchoscopes are available in various sizes, the smallest being 1.8 mm, which can fit through a 2.5 mm internal diameter (ID) endotracheal tube. The apparatus allows continuous oxygen supplementation directly into the airways, as well as suctioning, except with a 3.5 mm diameter or smaller fiberoptic laryngoscope.

It can be performed during local or general anesthesia and spontaneous breathing. Before the procedure the correct size endotracheal tube should be passed on to the bronchoscope as a sleeve, later to be passed into laryngeal inlet directed by the tip of the bronchoscope placed in the trachea. The patient is placed in the supine position with the head in a neutral position to prevent the epiglottis from obstructing the view of the glottic aperture. The passage of the flexible bronchoscope into the glottis is more easily achieved using the nasal route because a midline position can be more readily assured. Using the oral route, the fiberoptic bronchoscope has to be passed through the midline of the mouth. A bite block keeps the jaws open and allows a central entrance point for the bronchoscope. The tip of the bronchoscope should be gradually advanced under direct vision until recognizable structures are seen.

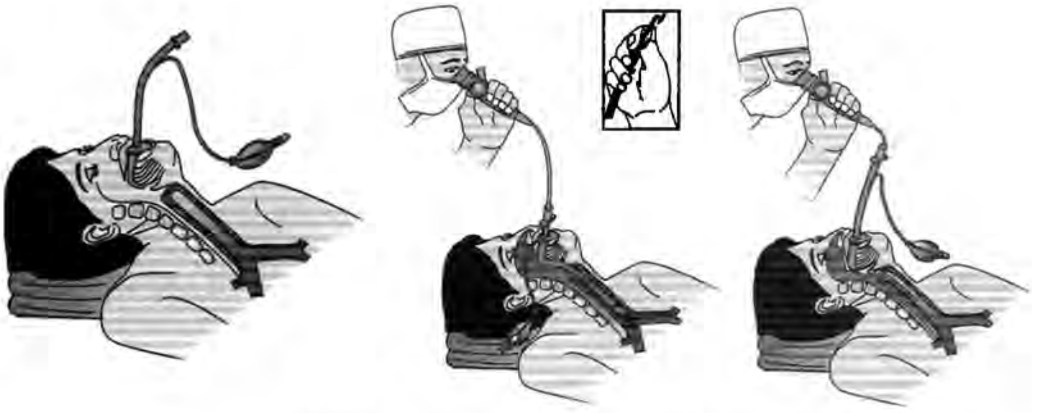


Fig. 4.14: Oral approach for fiberoptic intubation

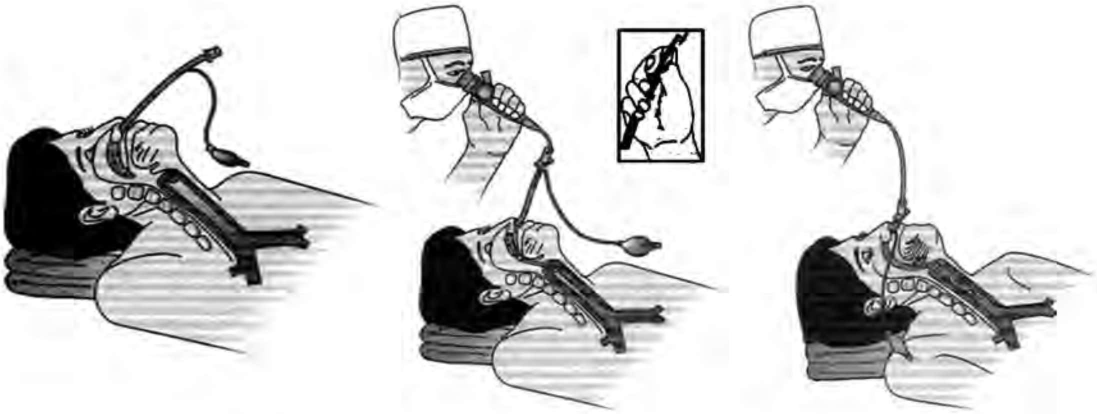


Fig. 4.15: Nasal approach to fiberoptic intubation

Once the tip of bronchoscope is past the vocal cords and placed in trachea, the endotracheal tube is passed into trachea and bronchoscope removed. Tube placement is checked using auscultation over the lung fields/and or by connecting to end tidal CO_2 monitor.

Bag mask ventilation with or without tracheal intubation can be required at any time in case of difficulty in maintaining adequate ventilation.

Fiberoptic intubation provides the advantages of direct visual guidance. However, emergency situations when vomitus, blood or copious secretions are present, it may be quite difficult. The technique requires practice under close supervision.

Prism Devices (Hufman Prism) or Dental Mirror

These simple devices can be useful in limited cases to visualize the laryngeal inlet. In presence of full stomach it is difficult to avoid vomiting.

Lighted Stylet or Lightwand

They are illuminated introducers or lightwand and their use in children below the age of 5 years has been described. The smallest tube that can be used is 5 mm of diameter. In dim light the lightwand loaded with a tube is passed through the nose or mouth. Upon proper positioning at the laryngeal inlet in the midline, a bright chery red organ can be seen in the region of the cricothyroid membrane. The endotracheal tube is then advanced over the tube into the trachea.

All these blind techniques benefit from the presence of end-tidal CO_2 measurement as means of confirming the corret placement of the tube.

Retrograde Translaryngeal Intubation

The technique consists of puncturing the cricothyroid membrane with a needle directed cephalad and then feeding a guidewire through the needle until the wire emerges from the nose or mouth. The wire is used as a guide for insertion of the endotracheal tube. Once the tube is in the trachea, the wire can be withdrawn. The maneuver is difficult to perform and requires an experienced operator.

Transtracheal Ventilation

Transtracheal ventilation can be performed by threading a small-bore plastic catheter into the lowe cervical trachea through a needle, after the pretracheal soft tissue has been anesthetized. The needle is then removed and the catheter fixed by tape or suture, or both. The tip of the catheter is positioned 2-3 cm above the carina in order to avoid accidental selective bronchial intubation.

The catheter positioning allows the application of jet ventilation.

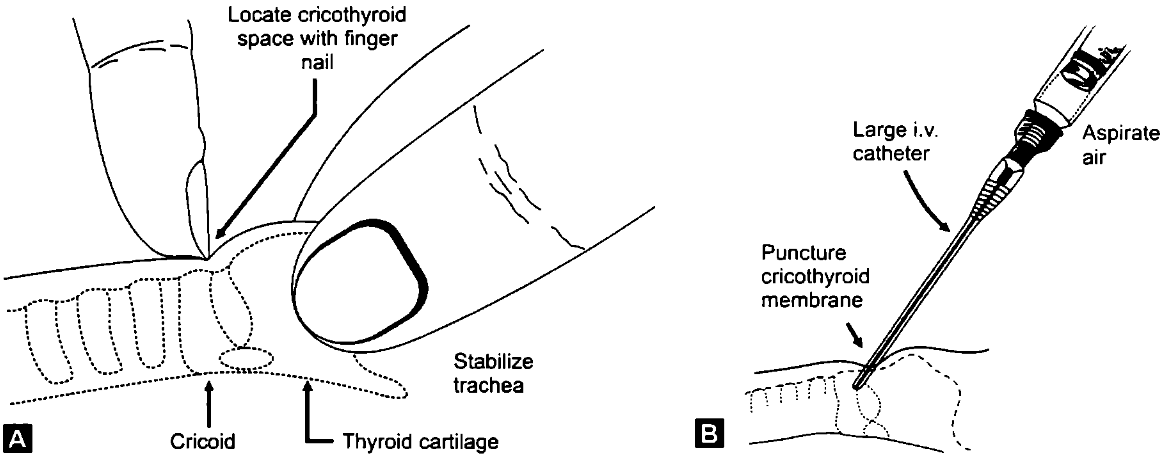
Surgical Access of the Airway

- Cricothyroidotomy
- Tracheostomy

Percutaneous Cricothyroidotomy

Cricothyroidotomy is a life-saving technique which can resolve severe and life-threatening situations as massive facial trauma, oropharyngeal hemorrhage, foreign body or severe upper airway obstruction. It is to be used only in emergency and all the physicians should be familiar with the technique. The method may easily damage cricothyroid cartilages because the cricothyroid membrane is of small width in infants and children. It can result in subsequent laryngeal stenosis and permanent damage to speech.

The technique requires the head and the neck to be extended in the midline and cricothyroid membrane to be located between the inferior margin of thyroid cartilage and superior edge of cricoid cartilage, with fingertip. The trachea is immobilized between the thumb and index finger and cricothyroid membrane is punctured using a large-bore needle or intravenous catheter (12 to 14 gauge, depending on the patient's age). The needle or catheter is advanced obliquely with 20-25" angle into the trachea towards the carina. Aspiration of air using a syringe confirms the correct positioning into the trachea. In cases of catheter-needle use, this is advanced into the trachea after discarding the needle in order to avoid injury. Ventilation can be carried out by use of a 3 mm adapter attached to any intravenous catheter (Figs 4.16 and 4.17).



Figs 4.16A and B: Steps for performing cricothyroidotomy

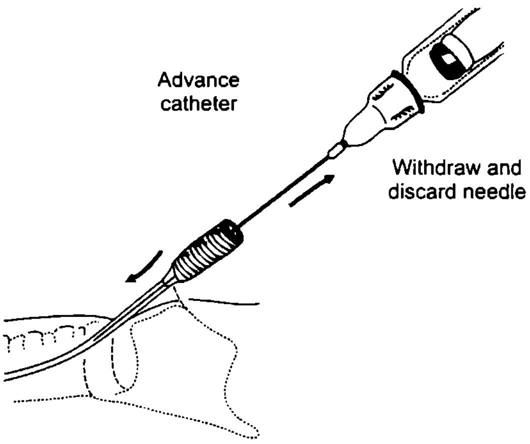


Fig. 4.17: Step for performing cricothyroidotomy

The technique provides only a means for oxygen insufflation and does not provide adequate ventilation. With inadequate alveolar ventilation but temporary oxygenation, hypercarbia is generally well tolerated by healthy children until more effective ventilation is established. Jet ventilation through the catheter has been successfully used even though very serious morbidity (massive subcutaneous emphysema or pneumothorax) and mortality may result.

In older children, in desperate conditions, a small horizontal incision over the cricothyroid membrane can allow a standard tracheostomy or an endotracheal tube be positioned into the tracheal lumen. The maneuver is difficult and dangerous to perform in infants and young children due to the small size of the trachea and the potential damage to the nearby neurovascular structures.

Interest swang away from tracheostomy with the advent of prolonged nasotracheal intubation in children. It is now swinging back and tracheostomy is becoming more frequent again. If the early decannulation can be achieved in less than 3 weeks, then complications are fewer.

Tracheostomy

Tracheostomy is no longer used as an emergency treatment and in long-term ventilation tracheal intubation has replaced tracheostomy particularly since the introduction of soft, long-lasting, nontoxic endotracheal tubes which are suitable for long term use, being well tolerated by the trachea (see chapter on tracheostomy).

Today tracheostomy is limited to conditions such as tracheal stenosis and iatrogenic injury to the upper airway, impossibility of intubation, in laryngeal disruption and complex craniofacial injury, in basilar skull fractures with cerebrospinal fluid leak and/or nasal fractures or deformity which contraindicate a nasotracheal tube, in arch bars and jaw wiring, and in chronic patients needing some ventilatory support.

In newborns, infants and young children, tracheostomy is generally avoided, if possible because of the potential damage (severe reduction of tracheal diameter) due to the smaller size of child's trachea compared to that of adult. However, when indicated tracheostomy can be performed in very small premature babies.

Difficult Intubation due to Laryngeal and Tracheal Obstruction

The visualization of vocal cords is possible but the passage of the tube into the trachea is difficult due to edema, inflammation, anomalies or presence of foreign body in laryngeal inlet, subglottis and cricothyroid region. In cases of visible foreign body, its removal using laryngoscope and forceps or using a fiberoptic laryngoscope is useful to restore patency of glottis. In cases of edema, inflammation or patent anomalies, the possibility to use semi-rigid tubes of progressive caliber can allow the positioning of the tube in trachea.

Having visualized laryngeal inlet by laryngoscope during general anesthesia in spontaneous breathing, a semi-rigid tube of suitable diameter is advanced into the larynx, dilating it progressively. Once a safe airway and sufficient oxygenation have been assured, the patient can be given muscle relaxant. Well lubricated progressive size of tubes are positioned pressing on stenotic area until a maximal size is introduced according to the normal anatomy and stenosis. The patient is subsequently intubated with a common soft tube (PVC or silicon rubber) using 1/2 caliber less than the maximum reached during dilation and artificially ventilated or maintained in spontaneous breathing (CPAP) in both cases using a PEEP level 5-10 cm of H_2O. In cases of CPAP, pressure support (5-10 cm of H_2O) can be applied in order to overcome tube resistance. Good results have been obtained, in our experience, using Volume Support Ventilation. This method allows a preset tidal volume to be maintained using the minimal inspiratory pressure. In cases of apnea, the ventilator switches automatically to PRVC (Pressure regulated volume control) ventilation.

Mild edema, e.g. postintubation edema in anesthesia, and inflammatory stenosis (e.g. acute laryngitis) resolve spontaneously in 3 to 5 days. Improved airway size is indicated by increasing airleak around the tube.

In cases of difficult extubation after long term ventilation, and suspected subglottic or tracheal stenosis the dilation maneuver can be repeated after 3-4 days for two to three times (over 20-25 days). If subglottic stenosis persists after 1 month, airway stent placement or surgical treatment has to be considered.

Intubation Failure

In case it is absolutely impossible to intubate, it is necessary

- To continue assisted ventilation by mask (to use laryngeal mask, sufficient experience is acquired, it is difficult to use in children under 2 years and contraindicated in full stomach patient and in emergency); to wake up the patient and to restore spontaneous breathing as soon as possible;
- To be ready to perform immediate cricothyroidotomy or tracheostomy.

American Society of anesthesiologist have a difficult airway protocol endorsed by difficult airway society as shown in Fig. 4.18.

SUMMARY

Airway management of pediatric patient can be tricky if a preassessment has not been performed for airway evaluation to detect any anticipated problems. Past history of mechanical ventilation, prolonged intubation, upperairway infections, airway surgeries is very important. Airway should be managed by a pediatrician profficient in airway opening, using airway adjuncts, bagmask ventilation as well as performing endotracheal intubation. In rare circumstances, situation of difficult intubation is faced. This problem should be dealt with an airway expert, who may need to perform fiberoptic oro or nasotracheal tube. In emergency situations cricothyrotomy or emergency tracheostomy may be required. Institutions should have a working protocol for difficult intubations.

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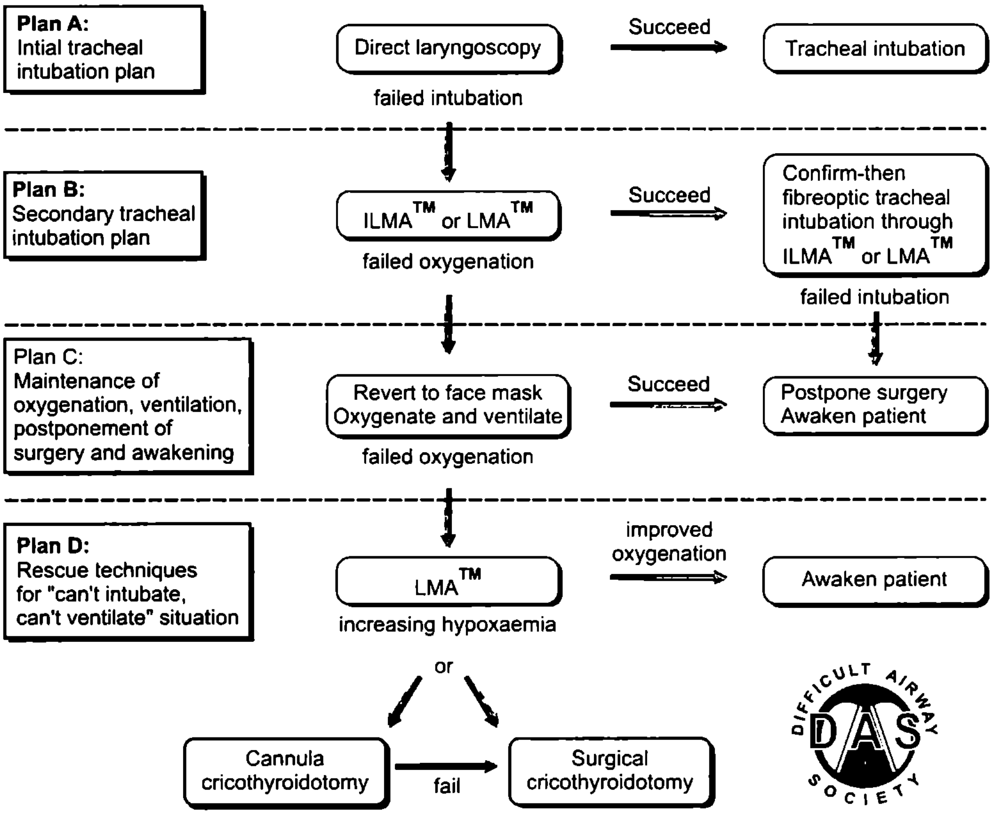
Plan A:
Intial tracheal intubation plan
Direct laryngoscopy
Succeed
Tracheal intubation
failed intubation
Plan B:
Secondary tracheal intubation plan
ILMA™ or LMA™
Succeed
Confirm-then fibreoptic tracheal intubation through ILMA™ or LMA™
failed oxygenation
failed intubation
Plan C:
Maintenance of oxygenation, ventilation, postponement of surgery and awakening
Revert to face mask
Oxygenate and ventilate
Succeed
Postpone surgery
Awaken patient
failed oxygenation
Plan D:
Rescue techniques for "can't intubate, can't ventilate" situation
LMA™
improved oxygenation
Awaken patient
increasing hypoxaemia
or
Cannula cricothyroidotomy
fail
Surgical cricothyroidotomy
DIFFICULT AIRWAY SOCIETY
DAS

Fig. 4.18: Difficult airway protocol

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CHAPTER

5

Transport of a Critically Ill Child

Praveen Khilnani, Rajiv Chhabra

When it comes to transporting a critically ill or unstable child or a neonate, most of the adult physicians, health care personnel are uncomfortable due to complex issues involved regarding physiological differences between the infant and the adult patient (such as airway anatomy, resistance, various lung parameters, oxygen consumption, age related cardiovascular variables, cardiopulmonary interactions), temperature regulation and most of all drug dosages. An efficient and good quality transport program is a key to success of any neonatal or pediatric critical care unit. Care of a neonate or a child during transport should be equivalent to that provided in an intensive care setting for safe transport.

ORGANIZATION OF A CRITICAL CARE TRANSPORT SYSTEM

Depending on the distance and geographical factors one or both modes of transportation may apply.

Ground Transport

Basic life support ambulance, or a mobile critical care transport unit are available.

Air Transport

Helicopter or a fixed wing jet plane transport may be used.

COMPONENTS OF A NEONATAL AND PEDIATRIC CRITICAL CARE TRANSPORT PROGRAM

Transport Dispatch System

An efficient transport communication system is must.

Transport dispatch center receives transport call from referral hospital/pediatrician/physician. This center can be located at the emergency department, or preferably in the pediatric/neonatal ICU, where a call can be received and directed to the appropriate pediatric or neonatal intensivist. A dedicated transport phone for incoming calls only is a good model to have in any pediatric or neonatal ICU for uninterrupted emergency transport requests 24 hours a day.

Communication with Neonatal or Pediatric Intensivist (The Intensivist)

Dispatch center forwards the call to the intensivist leading to physician (pediatrician) to physician (intensivist) communication regarding acceptance of the patient, and activation of transport process. Accepting intensivist receives patient information regarding medical condition, treatment given, and results of laboratory/radiological investigation from the referring institution. Medical advice regarding ongoing treatment is given by the accepting pediatric intensivist till transport team reaches the referral hospital. In addition, nurse to nurse communication regarding treatment details is very important, for accurate transfer of patient information. Information received and treatment advised should be documented on patient information form.

Response Time

Time that it takes for the transport team to be mobilized and leaving for referral institution after the transport call is received. Response time of under 30 minutes may be acceptable.

Critical Care Transport Team

Fundamental to team composition is the presence of aggregate knowledge and skill (in team members) required to transport a critically ill child safely, and ability to assess the need and to perform procedures such as CPR (cardiopulmonary resuscitation) endotracheal intubation, mechanical ventilation, drainage of tension pneumothorax, endotracheal suctioning, bronchodilator therapy, as well as vascular/intraosseous access, fluid therapy and vasopressor administration as deemed necessary.

In the western critical care transport programs, a nurse, respiratory therapist, and paramedic, or a nurse paramedic team may be sufficient as long as proper training and experience exists.

In the Indian setup with lack of trained paramedics and trained critical care nurses, a team consisting of a pediatric registrar and a nurse and ambulance driver is usually practical. Neonatologist, or a pediatric intensivist may be required in patients with unstable hemodynamic status, unstable airway, or in children requiring multiple interventions during transport. PALS/APLS certification for all members of transport team is necessary.

TRAINING AND SKILLS FOR TRANSPORT TEAMS

Following are the recommendations based on American academy of pediatrics guidelines on neonatal and pediatric transport.

General curriculum for all transport teams includes training in:

- Interpretation of X-rays
- Interpretation of common laboratory investigations
- Pharmacotherapy
- Fluid therapy
- Equipment training
- Legal issues
- Documentation

Other issues as applicable:

- Transport physiology
- Infection control
- Vehicle safety
- Public relations
- Continuous quality improvement

Following is a sample of *training and skills* components necessary for pediatric and neonatal transport teams.

Pediatric Critical Care Transport Team

- PALS certification is a must for all the members.

Technical Skills

Proficiency in following procedures:

- Endotracheal intubation
- Bag-mask ventilation
- Intraosseous line placement
- Needle thoracostomy
- Defibrillation and cardioversion
- Aerosol treatment
- Setting up transport ventilator
- Use of oxygen therapy devices (masks and cannulae).

Preferred Technical Skills

- Central venous line placement
- Arterial puncture
- Chest tube placement

Cognitive Skills

Recognize and manage:

- Cardiopulmonary arrest
- Airway obstruction
- Respiratory failure
- Airleak
- Status asthmaticus
- Shock
- Congestive heart failure
- Cardiac dysrhythmias

- Seizures
- Altered mental status
- Status epilepticus
- Increased intracranial pressure
- Multiple trauma/Burns
- Toxic ingestions
- Hematological emergencies
- Metabolic disorders including diabetic ketoacidosis
- Near drowning and other global hypoxic ischemic injuries
- Sepsis and other life threatening infections.

Neonatal Critical Care Transport Team

- PALS/NALS certification is a must for all the members.

Technical Skills

Proficiency in:

- Bag-mask ventilation
- Intravenous line placement
- Umbilical venous line placement
- Needle thoracostomy
- Setting up transport ventilator
- Use of oxygen therapy devices (mask, cannulae)
- Arterial puncture
- Administer surfactant

Preferred Skills

- Chest tube placement
- Intraosseous needle placement
- Peripheral arterial line.

Cognitive Skills

Ability to recognize and treat:

- Cardiopulmonary arrest
- Respiratory failure from common neonatal cardio-respiratory disorders
- Air leak
- Congenital heart disease
- Shock
- Sepsis
- Omphalocele and gastroscheisis
- Intestinal obstruction/perforation/common surgical problems
- Birth injuries
- Hypoxic ischemic encephalopathy
- Neonatal seizures
- Intracranial bleeding
- Metabolic disorders
- Coagulopathies
- Common malformation syndromes
- Marginal viability

Transport Process

Upon Arrival to Referral Institution

Transport team members should have planned approach and division of responsibilities. Clinical condition and main interventions should be documented. Usually pack and go policy after initial stabilization is effective.

Consent

An informed consent needs to be obtained from the parents of the minor by one of the team members.

Assessment and Stabilization

Initial history and rapid cardiopulmonary assessment needs to be performed. Airway must be secured and endotracheal tube position and potency must be ensured. If needed suction before leaving may be performed. Adequate ventilation should be ensured. Intravenous access needs to be properly secured and ongoing fluid and vasopressor therapy should be continued. Nasogastric tube and foley catheter should be secured as applicable. Before leaving a set of vital signs such as oxygen saturations, heart rate, blood pressure, and temperature should be documented.

Call Back to Prepare the PICU/NICU

Before leaving, clinically relevant information regarding the patient should be communicated to the receiving unit, such as vital signs, blood gases, ventilator settings, vaso-pressor drip doses. Besides this arrangements for CT scan, central line placement, arterial line placement, subspecialist consultations, arranging for operation theater, need for O negative blood, etc. should be clearly communicated.

Expected time of arrival (ETA) should be notified to the receiving unit. *Any adverse events should be recorded and treated during the transport en route.*

Table 5.1: Equipment

Larger equipments

- Transport incubator, or stretcher if patient weighs >5 kg
- Ventilator and humidification apparatus
- Monitor:
  - Heart rate, electrocardiogram and respiratory rate (preferably with recorder)
  - Blood pressure (systolic, mean, diastolic and waveform display)
  - Pulse oximeter
  - Portable suction unit,
  - Oxygen (FIO_2 monitor)
  - Temperature probe
  - Defibrillator, cardioverter, infusion pumps with high (1000 ml/H) and low (0.1 ml/H) flow
  - Portable oxygen cylinder
- Air oxygen blender (21–100% O_2) with flowmeter up to 15 L/min

Other desirable equipment

- End tidal CO_2 monitor and intracranial pressure monitor

Table 5.2: Smaller transport equipment (May be packed or placed in a tray)

Various sizes of

- Oral/nasal airway
- Laryngeal mask airway
- Laryngoscope: straight and curved
- Masks (neonatal and pediatric)
- Self-inflating resuscitation bag
- Anesthesia bag (C-Circuit)
- Endotracheal tubes (cuffed and uncuffed) (2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5 mm)
- Suction catheters (6, 8, 10, 12 fr)
- Air filters
- Tonsillar suction
- Thoracostomy set
- Emergency tracheostomy set
- Chest tubes (10, 12, 16, 20 fr)
- Cervical collar
- Intravenous cannulae (18, 20, 22, 24 g)
- Tape/armboard/splints/connecting tubings/threeway stopcocks
- Intraosseous needles
- Central line sets (double and triple lumen 4 fr, 5.5 fr, 7 fr)
- Heparinized saline (heplock fluid)
- Intravenous fluids
- Normal saline
- Ringers lactate
- Dextrose, 5%, 10%, 25%
- Isolyte P or D 5 1/4 NS
- Hemacel/Hetastarch
- Various medications

Table 5.3: Oxygen cylinder duration during transport

Flow L/min	*E tank Duration (hours)*	*H tank Duration (hours)*
2	5.1	57.51
3	3.4	38.3
4	2.5	28.7
5	2.0	23.0
6	1.7	19.1
7	1.4	16.4
8	—	14.4

Transport Equipment and Medications

Various large and small portable equipments are listed in Tables 5.1 and 5.2.

Table 5.3 shows the duration of oxygen flow from small (E) and large (H) oxygen cylinder.

Aeromedical Transport

A knowledge of altitude and flight physiology is essential for all members of an aeromedical transport team. Following chapter discusses the clinical significance of factors operative at high altitude as it affects the neonatal and pediatric transport.

Two most common gas laws of physics apply: *Boyles law and Daltons law.*

Boyle's Law

Volume of a given gas varies inversely with its pressure $P_1V_1 = P_2V_2$.

As the aircraft ascends atmospheric pressure goes down (Table 5.4) so the volume of gas in an enclosed space will expand and reverse is true when aircraft descends.

This applies to helicopters and unpressurized aircrafts. Helicopters flying 2 to 3000 feet above ground will cause 10 to 15 percent expansion which is usually insignificant.

At 8000 feet gas expansion will be 30 percent. This (effective cabin altitude) is equivalent to pressurized aircraft flying at 35 to 40,000 feet. Clinically this affects endotracheal tube cuff pressure, body cavities such as stomach, intestines, middle ear, sinuses, and a closed pneumothorax and intravenous flow rates. Other potential spaces include intracranial space, brain and subcutaneous tissue.

Table 5.4: Altitude related effects

Altitude	Barometric pressure	Temp C	Temp F	Gas expansion ratio
0	760	15	59	1.0
2000	706	11	51.8	1.1
5000	632	5.1	41.2	1.2
8000	565	– 0.9	30.4	1.3
10000	523	– 4.8	3.4	1.5
15000	429	– 14.7	5.5	1.8
18000	380	– 20.7	– 5.2	2.0
20000	349	– 24.6	– 12.3	2.4
25000	282	– 34.5	– 30.1	2.7
30000	228	– 44.4	– 47.9	3.3
40000	141	– 56.5	– 69.7	5.4
50000	87	– 56.5	– 69.7	8.7

Daltons Law

Total pressure exerted by a gas mixture equals to sum of individual partial pressures of all gases in the mixture $P_t = P_1 + P_2 ... P_n$

In room air percentage of oxygen is 20.95 percent at sea level. Barometric pressure is 760 mm. So partial pressure of oxygen at sea level is;

$$PO_2 = 20.95\% \times 760 \text{ mmHg} = 159.22 \text{ mmHg}$$

(say 160 mmHg)

(Pressure of nitrogen 593 mmHg, other gases 7 mmHg)

(Total atm pressure-160 + 593 + 7 = 760 mmHg)

At 10,000 feet the percentage of oxygen remains 20.95 percent, but the total atmospheric pressure is 523 mmHg, therefore partial pressure of oxygen falls to 110 mmHg. (Nitrogen 408 mmHg, other gases 5 mmHg) (Total atm pressure-110 + 408 + 5 = 523 mmHg).

Effects of increasing altitude on alveolar and arterial oxygen and carbondioxide are shown in Table 5.5. This is calculated by the alveolar arterial oxygen gradient. The more the blood shunting from the alveoli without picking up oxygen (collapsed alveoli), collaterals by birth, the greater will be the gradient (alveolar arterial difference).

$$\text{A-a } (O_2) = (FiO_2\ \%100) \times (\text{Patm-47 mmHg}) - (PaCO_2/0.8) - (PaO_2)$$

Cabin Altitude

Protection against influences of changing altitude is done by creating a cabin altitude by pressurizing the atmosphere in the aeroplane. About 25 percent of persons will become symptomatic at 8000 feet. Nearly everyone will be symptomatic at 12,000 feet (altitude sickness). Any accidental decompression will cause hypoxia and expansion of gas cavities. So all catheters, chest tubes, and nasogastric tubes should be unclamped.

Table 5.5: Effects of altitude on oxygenation

Altitude (Ft)	Barometric pressure	PAO_2	PaO_2 (mmHg)	$PaCO_2$	Oxygen saturation (%)
Sea level	760	159.2	103	40	98
8000	565	118.4	68.9	36	93
10000	523	109.6	61.2	35	87
15000	429	89.9	45	32	84
18000	380	79.6	37.8	30.4	72
20000	349	73.1	34.3	29.4	66
22000	321	67.2	32.8	28.4	60

PAO_2—Alveolar partial pressure of oxygen.
PaO_2—Arterial partial pressure of oxygen.
$PaCO_2$—Arterial partial pressure of carbon dioxide.

PREVENTION OF COMPLICATIONS DURING AIR TRANSPORT OF PEDIATRIC AND NEONATAL PATIENTS

Gas Expansion

1. Insert orogastric or nasogastric tubes open to air in every infant and in any child who may experience gastrointestinal symptoms or may be at risk for vomiting.
2. Avoid use of cuffed endotracheal tube. If cuff is used consider using water for filling the cuff.
3. Ensure that chest tube, endotracheal tubes, and other artificial vents are patent.
4. Suction airway well before and during transport.
5. Reevaluate for extrapulmonary air. Carry a transillumination device and have a needle thoracentesis device available.
6. Request, if possible, to fly at a lower altitude for patients with trapped gases (pneumothorax, pneumoperitoneum, bowel obstruction).

Decreased Partial Pressure of Oxygen

1. Before leaving the referral hospital
   a. Ensure that the child is as optimally oxygenated as possible.

   b. Correlate oxygen saturation with PaO_2.
   c. Check placement and stabilization of the endotracheal tube.
2. En route
   a. Increase FiO_2 to keep saturation of more than 95 percent.
   b. FiO_2 required can be calculated as follows:
      - FiO_2 required = (FiO_2 × BP1/BP2)
      - FiO_2 = current FiO_2
      - BP1 = current barometric pressure
      - BP2 = altitude barometric pressure

Stresses of Flight

Following stresses have been identified by several authors and various organizations:

- Barometric pressure
- Hypoxia
- Temperature
- Dehydration
- Noise
- Vibration
- Gravitational forces
- Fluid leakage out of intravascular spaces (third spacing)
- Fatigue.

Transport team members are equally affected with these stresses as is patient. Ear plugs, and plenty of fluids for the transport personnel and earplugs as applicable, adequate fluid therapy, close attention to pneumothorax, pneumoperitoneum, warming and extra oxygen can usually overcome these stresses.

FURTHER READING

1. Guidelines for air and ground transport of neonatal and pediatric patients: 2006 (3rd edition) American Academy of Pediatrics section on Transport Medicine; Edited by George A Woodward MD, MBA, FAAP.
2. Khilnani P, Chhabra R. Transport of critically ill children: How to utilize resources in the developing world. Indian J Pediatr 2008;75(6):591-98.

APPENDIX

TRANSPORT MEDICATION CARD AND USEFUL MISCELLANEOUS INFORMATION

This chart contains useful information and doses of various emergency drugs.

CARDIAC ARREST

1. Airway, breathing, circulation
2. 100% oxygen
3. Medications

Epinephrine

Newborn

0.1 ml/kg IV, ET (1:10000)

Child

First dose:	0.1 ml/kg IV, IO (1:10000) 0.1ml/kg ET (1:1000)
Subsequent doses:	0.1 ml/kg IV, IO, ET (1:1000)

Adult

Initially 1 mg IV every 3 to 5 min escalating to maximum of 1 mg/kg every 3 to 5 min; 1to 5 ml IV, ET (1:10000)

Atropine

0.02 mg/kg IV, ET < IM (minimum, 0.1 mg; maximum 1.0 mg)

Dextrose

Newborn:	D10W 2-4 ml/kg IV, IO
Child:	D25 2-4 ml/kg IV, IO
Adult:	D50 1 ml/kg IV, IO

Bicarbonate 1 meq/kg IV or (0.3 × kg × base deficit) (maximum 50 meq)

Defibrillate

Pediatric:	2 J/kg, then 4 J/kg (asynchronous)
Adult:	200 J, then 200-300 J, then 360 J

Cardioversion

0.5 J/kg (synchronous)

ENDOTRACHEAL (ET) INTUBATION

Age	*ET size*
< 28 week	2.5 mm/ID
28-38 week	3.0 mm/ID
newborn	3.0-3.5 mm/ID
6 month to 1 year	4.0 mm/ID
> 1 year	4 + age in years divided by 4

GLASGOW Coma Scale

Standard		**Pediatric**
Eye opening		
Spontaneous	4	Spontaneous
To voice	3	To speech
To pain	2	To pain
None	1	None
Verbal		
Oriented	5	Coos and Babbles
Confused	4	Irritable cries
Inappropriate words	3	Cries (pain)
Incomprehensible	2	Moans (pain)
None	1	None
Motor		
Obeys commands	6	Spontaneous movement
Purposeful (pain)	5	Withdraws (touch)
Withdraws (pain)	4	Withdraws (pain)
Flexion (pain)	3	Abnormal flexion
Extension (pain)	2	Abnormal extension
None	1	None
Total (3-15)		

ANALGESIA AND SEDATION

Morphine	0.1 mg/kg IV, IM
Meperidine (Pethidine)	1 mg/kg IV, IM
Midazolam	0.1 mg/kg IV, IM
Fentanyl	1 to 10 microgram/kg IV

REVERSAL AGENTS

Naloxone	0.1 mg/kg IV, IM, ET (> 20 kg = 2 mg)
Flumazenil	0.01 mg/kg IV (> 20 kg = 0.2 mg)

ANTIBIOTICS

Acyclovir	10 mg/kg/dose
Ampicillin	25-100 mg/kg/dose
Amikacin	7.5 mg/kg/dose
Cefotaxime	50 mg/kg/dose
Ceftazidime	30-50 mg/kg/dose
Ceftriaxone	25-75 mg/kg/dose
Cefuroxime	25-50 mg/kg/dose
Gentamicin	1.7-2.5 mg/kg/dose

Oxacillin	25-40 mg/kg/dose
Vancomycin	10 mg/kg/dose

ASTHMA, ANAPHYLAXIS, STRIDOR

Albuterol (Salbutamol)	0.5 ml (2.5 mg) in NS 3 ml nebulized
Adrenaline (Epinephrine)	0.01 ml/kg (1:1000) SQ max 0.5 ml
Nebulize	0.25 ml in 3 ml NS
Methyl prednisolone	1-2 mg/kg IV, IM
Terbutaline load	10 mics/kg/dose, IV, SQ
Drip	0.1-1.0 mic/kg/min
Dexamethasone	1 mg/kg/IV, IM
Hydrocortisone	2 mg/kg IV, IM
Diphenhydramine	1 mg/kg IV, IM

CARDIAC MEDICATION AND DRIPS

Adenosine	0.1 mg/kg rapid IV push (max 0.4 mg/kg or 12 mg)
Amrinone	3-10 mic/kg/min
Alprostadil (PGE1)	0.05-0.4 mic/kg/min IV
Amiodarone	5 mg/kg IV
Calcium chloride	10% 20 mg/kg (0.2 ml/kg slow IV)
Dobutamine	2-20 mic/kg/min
Dopamine	2-20 mic/kg/min
Epinephrine (adrenaline)	0.1-1 mic/kg/min
Milrinone	0.375-0.75 mic/kg/min
Nitroprusside	03-10 mic/kg/min
Norepinephrine	0.05-2 mic/kg/min
Propranolol	0.01 to 0.1 mg/kg IV over 15 min
Furosemide	0.5-1 mg/kg IV
Lidocaine	1 mg/kg (can repeat maximum of 3 mg/kg)
Drip	20-50 mg/kg/min (within 15 min of bolus)
Magnesium sulfate	25-50 mg/kg IV over 20-30 min (max 2 g)
Phenylephrine	0.01 mg/kg slow IV (max 5 mg) 0.1 mg/kg IM or SQ (max 5 mg) drip 0.1-0.5 mic/kg/min (titrate)
Procainamide	3-6 mg/kg over 5 min IV (max 100mg/dose)
Vasopressin (GI bleeding) bolus	0.3 U/kg (maximum 20) then 0.002-0.01U kg/min

(Calculation of drip = 6 x body weight in mg/kg to place in 100 ml) (1 ml/hr = 1 mic/kg/min)

ENDOCRINE

Glucose	D10W 4 ml/kg IV, IO(neonates) D25 W 2 ml/kg IV, IO (children)
Glucagon	0.1 mg/kg IV, IM, SQ (maximum 1 mg)
Insulin	0.1 unit/kg/hr

HYPERKALEMIA

Sodium polystyrene sulfonate (kayexalate)	1gm/kg PR, PO
Calcium chloride10%	20 mg/kg/dose = 0.2 ml/kg IV
Insulin	0.1 U/kg with glucose
Glucose D25	0.5 gm/kg = 2 ml/kg IV
Sodium bicarbonate	1-2 meq/kg IV (maximum 50 meq)

MALIGNANT HYPERTENSION

Labetalol	0.3-0.5 mg/kg/dose every 10 min (do not use if asthma or bradycardia)
Diazoxide	1-3 mg/kg rapid IV (max 150 mg)
Nifedipine	5-10 mg PO
Captopril	6.25-25 mg PO
	Resistant hypertension—Use Na nitroglycerin/ Na nitroprusside

SEIZURES

Lorazepam	0.05-0.1 mg/kg IV, IO
Diazepam	0.1 mg/kg IV 0.5 mg/kg PR
Midazolam	0.2-0.3 mg/kg IV
Phenobarbital	20 mg/kg at 1 mg/min
Phenytoin	20 mg/kg IV in NS at 1 mg/kg/min

INCREASED INTRACRANIAL PRESSURE

- 100% oxygen
- Hyperventilate to 25-30 mm Hg
- Keep head elevated in midline position
- Maintain adequate perfusion (avoid hypotension)
- Mannitol 0.25-0.5 gm/kg IV
- Lidocaine 1 mg/kg IV before intubation

RAPID SEQUENCE INTUBATION

- Oxygenate
- Atropine 0.02 mg/kg
- Lidocaine 1 mg/kg (if increased ICP or bronchospasm)
- Sedation (Normotensive)
- Thiopentone 2-5 mg/kg IV
- Midazolam 0.2-0.3 mg/kg IV

(Shock without head injury and status asthmaticus)

- Ketamine 0.5-2 mg/kg IV

HEAD INJURY

Thiopentone	2-5 mg/kg (if hypotensive reduce thiopentone)
Midazolam	0.2-0.3 mg/kg IV
Cricoid pressure	
Muscle relaxants	
Succinylcholine	1-2 mg/kg (do not use if potassium level increased or risk of malignant hyperthermia)
Vecuronium	0.1 mg/kg
Pancuronium	0.1 mg/kg
Atracurium (if liver failure/renal failure)	0.2-0.5 mg/kg IV

MISCELLANEOUS DRUGS

Charcoal	1 gm/kg PO/NG
Digoxin (digitalization)	< 40 week gestation: total 20 to 30 micro-gram/kg IV, IM Term-12 year: total: 30-40 micro-gram/kg IV, IM
Diphenhydramine	1mg/kg (IV, IM, PO)
Hydrocortisone	
Adrenal insufficiency	1-2 mg/kg bolus IV
Stress dose	0.25-0.5 mg/kg IV, IM
Metoclopramide	1-2 mg (antiemetic) IM, IV
Ipecac syrup	15 (child) to 30 ml (adolescent) PO
Nifedipine	0.25 mg/kg (sublingual)
Methylprednisolone	
Status asthmaticus	2 mg/kg then 1 mg/kg Q 6 hr
Spinal cord injury	30 mg/kg over 15 min, then 5.4 mg/kg/hr for 23-48 hours.
Surfactant:	
Beractant (Survanta) 4 ml/kg/dose ET	
Colfosceril palmitate tyloxapol (Exosurf)	5 ml/kg/dose ET
Tolazoline	1-2 mg/kg over 10-15 min IV followed by 0.2-0.5 mg/kg/hr
Vasopressin (GI bleeding)	0.3 U/kg bolus (aqueous 20 U/ml) IV (Oil 5 U/ml) IM

CHAPTER

Consensus Guidelines for Pediatric Intensive Care Units in India

Compiled by Praveen Khilnani (For IAP and ISCCM)

These guidelines have been developed jointly by Indian Society of Critical Care Medicine (ISCCM) Pediatric section and Indian Academy of Pediatrics (IAP) (intensive care chapter).

INTRODUCTION

Field of pediatric intensive care is rapidly growing in India. Number of intensive care units providing care to infants and children are also progressing at a rapid pace.

In year 2001, IAP intensive care chapter and ISCCM Pediatric section jointly took the initiative to develop such guidelines those can serve as a reference for health care institutions wishing to establish a new PICU or to modify an existing PICU.

After a great deal of discussion at the conferences and through mailing and active criticism and feedback with listed members, following consensus was developed.

Following guidelines are to be considered as guidelines in the strict sense and by no means an established standard of PICUs in India. As a resource, experience of those members who have worked extensively in western PICUs was also taken into consideration in addition to published guidelines in the medical literature. Care was taken to adequately develop and adapt the guidelines to be applicable in the Indian context.

Following is a description of specific guidelines regarding:

1. Unit design
2. Equipments
3. Organization and Staffing
4. Ancillary support services
5. Levels of PICU care and admission and discharge criteria.

A list of drugs recommended to be stored in PICU is also included at the end (Appendix).

UNIT DESIGN

PICU should be a separate unit from the Neonatal and Adult ICU dedicated to infants and children.[1] Unit design should take into consideration future adaptability and expansion and must maximize the resource of space, equipment, and personnel in a most affordable way as feasible for individual institution. No traffic to other departments should pass through the unit.

Unit should be located near lift with easy access to emergency department and operation theater, laboratory and radiology department. Doctor duty room as well as intensivist duty room/office should be close to PICU with intercom facility. Other facilities nearby should include a staff area with locker cabinets, a family waiting area to provide for at least one (preferably two) persons per admitted patient with bathroom, shower and telephone facility as feasible.

Size of the PICU

Ideal PICU size is not known but six to ten beds is desirable. PICUs less than 4 beds risk inefficiency and PICU greater than 16 beds may be difficult to manage, if not properly divided.[2] For total pediatric ward beds up to 25 a PICU of six to eight beds is ideal. Additional beds may be required if specialized surgery such as heart surgery, neurosurgery and trauma surgery cases are routinely done.

Room Layout and Bed Area

Room layout should allow actual visualization of all patients from central station. PICU cubicles should have sliding glass doors to allow full visibility. Patient area in open PICU should be 150 to 200 sq ft. In a cubicle, the minimum area should be 200 to 250 square feet with at least one wash basin for two beds, however, one for each bed is preferred. At least one, preferably two rooms should have an isolation capability with an area of 250 square feet with an ante room (separate area at least 20 square feet for hand washing and wearing mask and gown) and separate ventilation. Area around the bed should allow enough space for performing routine ICU procedures such as central lines, chest tube placement, as well as for easy access for portable X-ray machine, portable ultrasound, electrocardiograph and portable electroencephalograph machine.

An easy access to head end of the patient for emergency airway management is must on all beds. Wall and ceilings should be constructed of materials with high sound absorption capabilities. Wall oxygen outlets (two), air outlet (one), two suction outlets, and at least ten electrical outlets per bed are recommended for various equipments.[2,3] In rooms, windows are important to prevent a sense of isolation. Adequate lighting, child friendly wall-papering or paintings with soothing colors and curtains are desirable.

Power Supply and Temperature Control

Unit should preferably be centrally air conditioned and should have central heating for temperature control. In case of lack of central heating system, over head warmers should be available. Unit should have an uninterrupted power supply by means of backup power sources such as invertors and generators in accordance with load of various equipments.

Beds

Beds should have ability to maneuver head end and foot end as well as availability of two or more air/water mattresses to prevent bed sores. All beds must have a railing to prevent accidental fall of the child. Each bed should have an emergency alarm button to activate code system[3] in case of a cardiac arrest or other emergencies so that additional help can be immediately mobilized. An intercom at each bed is desirable. A cart at the bedside is important to hold personal belongings and required patient items.

Crash Cart (Resuscitation Trolley)

A crash cart with emergency drugs and portable monitor/defibrillator should be readily accessible. Zones should be provided for medication preparation, and cabinets should be available for the storage of medications and supplies.

A receptionist area is ideal to control visitation, so that all visitors must go by this area before entering.

This area should be monitored by security.

Central Station

A central station should provide visibility to all patient areas.[4] It should have ample area to have capacity for all necessary staff functions. Patient records should be easily available.

Adequate space for computers, printers and central monitors is essential. Ample space for doctors to write on patient files and space for unit secretarial staff is essential. At least two telephone lines should be available. A cordless telephone instrument is desirable. If possible, a telephone line dedicated to incoming calls only to facilitate critical care transport requests is desirable.

X-ray Viewing Area

A distinctive area in PICU should be chosen for viewing and storage of patient X-ray. An illuminated viewing box should allow viewing of several films.

Storage

Storage for vital supplies should be located within or closely adjoining to PICU. A refrigerator is essential for some pharmaceuticals. An area must be provided for storage of large patient care equipment items not in active use. An area must be provided for stretchers and wheel chairs.

Clean and Dirty Utility Room

Clean and dirty utility rooms must be separate rooms. The clean utility room should be used for the storage of clean linen. Dirty utility room must contain a separate sink. Covered bins must be provided for soiled linen and waste materials.

An area for emptying and cleaning bed pans and urine bottles is also necessary.

Waste Disposal

Mechanism of disposal of contaminated waste (segregation of garbage and contaminated medical waste) and adequate disposal of needles and sharp objects needs to be as per standard applicable pollution control guidelines.

Conference Room

A room for intensivist and staff for education, discussion of difficult cases and other necessary meetings related to quality improvement is desirable. This room should have a small library facility with ready access to important intensive care books, journals and policy manuals.

Stat Laboratory

A mini laboratory with arterial blood gas, electrolyte, blood sugar, urea, creatinine, prothrombin time, partial thromboplastin time, complete blood count and urine examination with gram stain should be considered adjacent to the PICU. Twenty four hour availability of on site or in hospital arterial blood gas is essential.

As an alternative to stat laboratory adjacent to PICU, a central main laboratory facility with a turn around time (reporting time) of less than one hour for stat laboratory test results is acceptable.

Equipment

The selection of equipment should be based on following criteria:

- Cost benefit analysis, accuracy and adaptability for pediatric population, ease of use for care givers, trouble shooting requirements, proven use on pediatric patients, maintenance requirements and biomedical support of the company and the hospital.
- Following is a list of essential and optional equipment for a tertiary level PICU[2,5] (Table 6.1).

Table 6.1: PICU equipment

Equipment	*Essential*	*Optional*
a. **Diagnostic equipment**		
Otoscope/ophthalmoscope		
Portable EEG	x	
Portable X-ray	x	
12 lead portable ECG	x	
Blood gas machine	x	
Glucometer	x	
Portable ultrasound	x	
Portable echo cardiogram	x	
b. **Procedural equipment**		
Emergency cart	x	
Emergency drugs (see appendix)	x	
Ventilators (volume/pressure/peep pressure support, low tidal volume (capacity 30 to 50 ml) with nebulizer, humidification and alarms)	x	
Noninvasive ventilator		x
High frequency ventilation		x
Nitric oxide		x
Heliox		x
Micro infusion pumps	x	
Defibrillator/cardiovertor	x	
Portable suction	x	
Pediatric ambu bag	x	
Mapleson anesthesia bag with circuit		x
T piece	x	
Pediatric laryngoscope (Curved and straight blades)	x	
Endotracheal tubes (2. 5-7 mm)	x	
Pediatric size masks	x	
Laryngeal mask airway	x	
Intubating flexile laryngoscope		x
Nebulizer	x	
Oxygen delivery devices	x	
Rebreather mask	x	
Nasal cannula	x	
Nonrebreather mask	x	
Oxygen hood (head box)	x	
Oxygen (portable) cylinders	x	

Contd..

Contd...

Equipment	*Essential*	*Optional*
Nasogastric tubes	x	
Heating and cooling blanket		x
Overhead warmer	x	
Procedure light (portable)	x	
Introsseous needles	x	
Multilumen central catheters (4, 5, 5. 5, 7 fr) 8 cm and 16 cm	x	
Cannulae for IV access and Arterial lines (24, 22 and 20 guage)	x	
General sterile trays (instrument set) and sets for:	x	
Chest tube		
Tracheostomy		
Cut down		
Suture removal		
Lumbar puncture		
Flexible bronchoscope		x
c. **Monitoring equipment**		
Transducers	x	
Rectal thermometer probe	x	
Glass thermometer	x	
Noninvasive blood pressure monitor	x	
Oxygen analyzer	x	
Portable monitor	x	
Pulse oximeter	x	
End tidal CO_2		x
Bedside monitoring with following capability:		
ECG	x	
Respiratory rate	x	
Temperature	x	
Arterial pressure	x	
Noninvasive blood pressure	x	
Central venous pressure	x	
Intracranial pressure		x
Arrhythmia alarms		x
Heart rate (high and low rate alarm)	x	
Apnea alarms,	x	
Memory, trends		x
Printout feature		x
d. **Miscellaneous equipment:**		
*Phototherapy		x
Overhead warmer	x	
Bedside table	x	
Over bed table	x	
IV pole	x	
Bedside chair	x	
Procedure stool	x	
Clocks	x	
Television	x	
Toys	x	
*Breast pump	x	
*Infant weighing machine	x	

*Some neonatal equipment is listed to facilitate care for small infants.

ORGANIZATION AND STAFFING

Medical Director/Intensivist Incharge[5]

Preferably a pediatrician trained and experienced in critical care of children with following responsibilities:

1. Establishing policies and protocols with the help of a group of experts including but not limited to pediatric consultants and subspecialists, nursing director, administration, laboratory and blood bank representatives.
2. Smooth functioning of PICU with implementation of policies and protocols including admission and discharge criteria.
3. Quality assurance and improvement (membership of hospital audit/quality improvement committee).
4. Advise administration regarding equipment needs.
5. Establishing teaching and training system of medical, nursing and ancillary staff.
6. Maintaining PICU statistics for mortality and morbidity.
7. Being member of infection control committee.

Staffing Requirements

Medical Staff

Round the clock postgraduate level pediatrician in PICU with good airway and pediatric advanced life support skills and active PALS certification.

Nursing Staff

Ventilated patient needs one pediatric/ICU trained nurse by the bedside. Very unstable patient (hypotensive/hypoxemic patient despite moderate support) may require two nurses by the bedside. Other unventilated/relatively stable patients (such as postoperative patients and ones admitted for overnight observation) may require only one nurse per 2-3 patients.

ANCILLARY SUPPORT STAFF

All PICUs must be regularly staffed by physiotherapists, dieticians and respiratory technicians for enhancing patient care. In addition, technicians, radiographers, and biomedical engineers should be available on a 24 hour (in hospital) basis for emergencies/problems that require immediate attention such as power failure, central gas supply problems, malfunctioning equipments, or need for urgent X-ray of chest in a patient with suspected pneumothorax.

Secretarial/clerical staff is essential to carry out communication as well as paper work necessary for smooth functioning of the unit. It is also essential to have cleaning staff that is efficient and sensitive to urgent patient care needs. Presence of social worker is desirable to help support families emotionally as well as financially in stressful circumstances.

LEVELS OF PICU CARE AND ADMISSION AND DISCHARGE CRITERIA[6-8]

Levels of PICU Care

Two levels are identified: level 3 and level 2:

Level 3 (tertiary) PICU can be organized with level 2 (step down/high dependency) service in nearby but separate area. In small private setups level 3 and level 2 care can be provided in one unit provided facilities and equipment as well as personnel described above is available.

Level 3 Care (tertiary level PICU)

Characteristics of level 3 care are as follows:

1. Defined admission, discharge policies.
2. Four to six ventilated beds.
3. More than 200 ventilated patients per annum.
4. Pediatric intensivist heading the unit.
5. One pediatrician with postgraduate training and experience in critical care present in PICU at all times.
6. Minimum one to one nursing on ventilated patients.
7. High level of monitoring possible in all patients.
8. 24 hour access to blood bank, pharmacy, pathology, operating theater, and tertiary level of imaging services.
9. Support staff, biomedical engineering, clerical-staff, technicians.
10. Educational and research activities.
11. Quality review/audit process in place.

Admission Criteria to Level 3 Care PICU [6,7]

1. All patients requiring mechanical ventilation.
2. Patients with impending respiratory failure:
    a. Upper airway obstruction
    b. Lower airway obstruction
    c. Alveolar disease
    d. Unstable airway
3. All pediatric patients after successful resuscitation.
4. Comatose patients:
    a. Meningitis, encephalitis,
    b. Hepatic encephalopathy
    c. Cerebral malaria
    d. Head injury
    e. Poisoning
    f. Status epilepticus
5. All types of shock/hemodynamic instability:
    a. Septic shock
    b. Hypovolemic shock
    c. Bleeding emergencies such as gastrointestinal bleeding, bleeding diathesis, disseminated intravascular coagulation.
    d. Cardiogenic shock: Myocarditis, cardiomyopathy, congenital heart disease
    e. Neurogenic shock.
    f. Multiple trauma.
6. Cardiac arrhythmias.
7. Hypertensive Emergencies.
8. Severe acid base disorders.
9. Severe electrolyte abnormalities.
10. Acute renal failure: Patients requiring acute hemodialysis, hemofiltration and peritoneal dialysis.
11. Postoperative patients:
    a. Requiring ventilation.
    b. Unstable patients.
    c. Postoperative patients after open heart surgery, neurosurgery, thoracic surgery and other patients after major general surgery with potential for respiratory/hemodynamic instability.
12. Patients requiring ECMO (Extracorporeal membrane oxygenation), nitric oxide therapy (if available).
13. Malignant hyperpyrexia.
14. Acute hepatic failure.
15. All posttransplant patients (if applicable).

Admission Criteria to Level 2 Care (stepdown/high dependency PICU)

1. All ward patients requiring close monitoring due to potentially unstable conditions.
2. Croup (laryngo tracheobronchitis) requiring oxygen.
3. Asthma requiring hourly nebulization /getting tired with increasing oxygen requirement/ mental status change.
4. All patients requiring more than 50% oxygen to maintain saturations.
5. Closed head injury/skull fracture admitted for observation.
6. Diabetes ketoacidosis with pH < 7. 2.
7. Patients with episodes of apnea.
8. Patients with significant abdominal trauma with suspected renal/splenic/hepatic injury
9. Severe dehydration with mental status change.
10. Postoperative patients after major surgery with significant postoperative pain/blood loss/ stress.
11. Patients recovering from critical illness (level 3 care), but requiring close monitoring.

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APPENDIX

DRUGS RECOMMENDED TO BE STORED IN PICU

A

Acyclovir
Adenosine
Adrenaline
Albumin 5%, 10%, 20%
Amiodarone
Amphoterecin
Ampicillin
Amrinone (if available)
Atracurium
Atropine
Augmentin

C

Calcium chloride
Calcium gluconate
Captopril
Cefoperazone
Cefotaxime
Ceftazidine
Ceftriaxone
Chlorpheniramine
Ciprofloxacin
Cloxacillin

D

Desmopressin
Dexamethasone
Dextran
Dextrose (5%, 10%, 50%)
Dextrose saline
Diazepam
Dobutamine
Dopamine
Droperidol

F

Fentanyl
Fluconazole
Flumazenil (if available)

H

Hemeccel
Heparin
HES (starch)
Hydralazine
Hydrocortisone

I

Insulin
Isolyte p

K

Kayaxelate
Ketamine
Ketorolac

L

Labetalol (if available)

M

Magnesium sulphate
Magnesium trisilicate
Mannitol THAM (Tris hydroxy amino methane)
Metronidazole
Midazolam
Morphine
Meropenem

N

Naloxone
Neostigmine
Nifedipine
Noradrenaline
Normal saline

P

Pancuronium
Penicillin
Pentazocin
Pethidine
Phenergan
Phenobarbitone
Phenytoin
Potassium chloride
Propofol
Propranolol

R

Ranitidine
Ringers lactate

S

Saline 3%
Sodium bicarbonate
Sodium nitroprusside
Streptokinase
Succinyl choline
Sucralfate

T

Thiopentone
Tiecoplanin
Trinitroglycerine

V

Vancomycin
Vasopressin
Vecuronium
Vitamin K

X

Xylocaine

CHAPTER

7

Monitoring in the Pediatric ICU

Praveen Khilnani, Jose Irazzuzta, Rajiv Chhabra

In this technology intensive field of critical care, monitoring is an integral part of intensive care, to detect potentially serious physiological derangements as early as possible, so that appropriate therapeutic intervention can be instituted to restore stability in a critically ill child.

Main goals of continuous monitoring of physiologic parameters in the pediatric intensive care unit (PICU) are early detection of organ system failure or complications related to illness or therapy. Trends in physiological parameters can guide the clinician regarding prognosis and possibly outcomes. In the last few years, a large variety of monitoring equipment has become available. Some of this technology has provided significant improvement in the care of patients, some has shown an improvement in only a selected group and in others, the efficacy remains to be proven.

This can get confusing to the pediatric intensivist with respect to relative merits and clinical efficacy and necessity of a particular monitoring equipment.

A good monitoring system should be patient friendly, with simple, reliable, reproducible, easy to read continuous display of parameters, with audio visual alarms, recording and storage capability. It should be cost beneficial and must have a service agreement with full technical support.

The principles of operation of any technology must be fully understood to know its capabilities and limitations. Human clinical interpretation of parameters displayed on the monitor is very important.

The most efficacious and probably most cost-effective monitoring of patient is the frequent assessment by a bedside nurse or a physician (Figs 7.1 and 7.2). Neurologic status, heart rate, respiratory rate, adequacy of air exchange, movements of the chest wall and breath sounds, temperature of the extremities, capillary refill, quality of the pulses, hourly urinary output, etc. can be assessed. A well-trained nurse/physician team can check these parameters several times in a reproducible form, document them, and integrate all information to assess the overall status of a patient. This type of "technology" is not available for purchase through a company representative. It is the product of a dedicated and specialized education process which can receive periodic checkups and unlimited upgrades, and is available in any country. Without a doubt this is the most valuable monitoring system in existence in critical care.

Fig. 7.1: Clinical observation of a critical patient by nurse by the bedside in PICU (*For color version see Plate 2*)

Fig. 7.2: Human monitoring (Bedside examination has no substitute) (*For color version see Plate 2*)

Although many clinical, physiological, and biochemical parameters are routinely monitored in the PICU, following discussion is limited to three main important systems that are routinely monitored in a critically ill child:

1. Cardiovascular system
2. Respiratory system
3. Neurological system

CARDIOVASCULAR MONITORING

The circulatory status can be assessed by: heart rate, quality of peripheral pulses and capillary refill, temperature, central pulses, urine output, and level of consciousness. Cardiorespiratory monitoring, invasive arterial and central venous pressure monitoring, automated non-invasive blood pressure monitoring and bedside echocardiography are part of the technologic armamentarium to monitor the cardiovascular system.

Cardiorespiratory Monitors

Cardiorespiratory monitors are part of the basic standard in the PICU.

Principle A sensor system consisting of electrodes is applied to the patient to detect electrical activity from the heart. This signal is amplified and displayed as waveform, i.e. electrocardiogram (ECG). A display of the rate and pattern of the chest wall movements is called pneumography. There is a wide variety of these monitors. The most important features are display of the ECG tracing and respiratory movement with at least two channels for invasive pressure monitoring. Most monitors come with a built in pulse oximeter and a non-invasive automated blood pressure monitor (Hewlett Packard, BPL, Ohmeda).

These monitors should allow for adjustment of the signal intensity, have a numeric read out, save information in memory, and transmit it to another monitor and/or central station if possible. Monitors must be equipped with audio and visual alarms for parameters that can be set to the particular needs of a patient, e.g. apnea at 10, 15, or 20 seconds. The possibility of printing the information stored on the monitor is a very attractive feature, but may not be affordable in all units. High and low rate alarms can be set on these monitors.

Troubleshooting Proper placement of electrodes is crucial. The skin must be clean and dry. Standard electrodes with lubricating conductive jelly may be used. The electrodes measuring impedance of the chest should be placed on each side of the chest. It should be remembered that the detection of chest wall movement does not necessarily reflect an effective volume, e.g. airway obstruction may not be detected even though chest movements are adequate. Certain types of electrodes may irritate the skin in some patients.

Hemodynamic Monitoring

This is indicated in any patient admitted to the pediatric intensive care unit (PICU) who is in shock, has respiratory failure, or has sustained an acute neurologic insult. Included in hemodynamic monitoring are heart rate and blood pressure as well as CVP and pulmonary capillary wedge pressure (PCWP) and, occasionally in postoperative cardiovascular patients, right atrial and left atrial pressures (RA and LA lines). Heart rate can be measured with conventional electrodes placed on the chest, which can also provide rhythm strips usually in lead II. The lead can be changed if indicated to evaluate for other dysrhythmias, but it should not substitute for a 12-lead electrocardiogram (ECG).

Blood pressure is determined invasively and non-invasively. The choice is determined by the instability of the patient, skill levels of the physicians, and ability of the staff to maintain such devices. Non-invasive blood pressure monitoring provides for manual or automatic repeated but intermittent readings of blood pressure. Whether one chooses a conventional sphygmomanometer or an ultrasonic/ Doppler device, appropriate cuff sizes are required to obtain an accurate blood pressure. The cuff should encompass approximately two thirds of the length of the part of the extremity from which it is measuring. The upper arm, lower leg, and upper leg offer the best sites for obtaining non-invasive blood pressures. Besides the cuff size, factors that affect peripheral blood flow or pulmonary vascular resistance or produce significant peripheral edema may result in abnormal values for non-invasively measured blood pressure.

Automated Non-invasive Blood Pressure (NIBP) Monitoring

Principle Non-invasive blood pressure measurements are done automatically using oscillometric principle, or a Doppler technique.

Oscillometry Equipment consists of an inflatable occlusive cuff connected via a double plastic tubing to an inflating pump and to a pressure transducer, e.g. Dinamap. Oscillations in the artery are produced after an automatic inflation, and deflation of the cuff. Oscillations detected are transformed into an electrical current, integrated into a microprocessor, and digitally displayed. The cuff inflates above the systolic pressure occluding the artery. As the cuff is deflated, the artery opens, blood spurts through, and there is detection of the oscillations which determines the systolic BP. The cuff pressure continues to decrease and the point where maximal oscillations are detected represents the mean arterial BP. As the cuff pressure decreases, there is a point where the artery remains open and the oscillations are uniform with minimal amplitude; this is the diastolic BP. This technique reflects mean arterial pressure fairly, accurately, but in comparison with intra-arterial pressures, it may show a higher diastolic pressure reading. It has a tendency to get a lower reading of high systolic blood pressure and a higher reading of low systolic pressures.

Doppler Ultrasonic Technique

It functions by ultrasonic detection of the arterial wall motion when the cuff is deflated. Audible sounds similar to Korotkoff sounds are emitted. It is described as being more reliable in cases of hypotension or shock, and being unaffected by artefacts created by patient motion or acoustics.

Troubleshooting: To avoid pitfalls, it is important to keep the cuff at the level of the heart, the width of the cuff should encircle at least two-thirds of the extremity, and kinking of the tubing should be avoided. A limb that has an arterial line or where an infusion is being administered should not be used.

Arterial Pressure Monitoring

Because of the technical limitations of non-invasive monitoring, invasive hemodynamic monitoring may be preferred. Sites commonly used to place catheters in an artery for invasive monitoring include the radial, ulnar, posterior tibial, and dorsalis pedis arteries (see section on procedures). Less frequently used are the femoral, axillary and brachial arteries and, when available, the umbilical artery. Arterial lines may be inserted either percutaneously or via cutdown if one is unsuccessful with percutaneous attempts. Before attempting to insert an arterial line one should ensure that collateral circulation exists if possible by performing an Allen test (for radial or ulnar lines). Once the catheter is properly inserted, a pressure transducer and pressure tubing are used to connect the catheter to the monitor. A continuous pressure waveform tracing can then be displayed on the monitor screen and should be displayed along with the simultaneous ECG tracing.

Principle Mechanical energy (the pressure that blood exerts on a transducer dome) is transformed into an electrical signal, it provides easy access to monitor arterial blood samples. Heparinized saline (1 unit of heparin/ml of saline) is used to flush the angiocatheter system continuously at 2 to 3 ml/hr to maintain patency and good arterial waveform display.

It is important to remember that because impedance increases in arteries distal to the aorta, a waveform with a higher spike will be seen in a peripheral artery than in a more central artery. This will produce a higher systolic pressure distally, but the mean arterial pressure (MAP) will not be affected. Mean arterial pressure is the driving pressure to perfuse the brain, the coronary arteries, the kidney, and the splanchnic bed; therefore, it is the measurement most often monitored in the PICU. The arterial waveform may be helpful in diagnosing hypovolemia (very narrowed and blunted dicrotic notch), determining the severity of cardiac dysrhythmias (pulsus alternans), and evaluating the effects of respirations (air trapping) or high pericardial pressure on blood pressure (pulsus paradoxus). Arterial lines also allow for the frequent sampling of blood for various laboratory tests including arterial blood gases, electrolytes, coagulation panels, and others as needed.

Complications from arterial catheterization are rare but may be very serious and require aggressive therapies. Bleeding and infection are relatively rare. Usually, direct pressure to the insertion site will reduce any further bleeding. Cutdowns may require resuturing or placing topical clotting material in the incision. Colonization around the insertion site may produce bacteremia and septicemia. The most serious complication is arterial thrombosis. This is seen in patients with low cardiac output states (shock), in those where heparin was not used in the flush solution, or in those patients who have required prolonged duration of catheter placement. Thrombosis necessitates the immediate removal of the catheter. The use of intravenous heparin or thrombolytic therapy or topical nitroglycerin paste is indicated if the extremity continues to have evidence of poor perfusion. Other complications include vascular spasm, cutaneous mottling, arterial tears, pseudoaneurysms, peripheral nerve damage, and arteriovenous fistula formation. Temporal artery sites are associated with retrograde flow into the carotid artery resulting in cerebrovascular accidents and therefore should be avoided. Decreased flow distal to an extremity site may result in serious necrosis of an extremity. Excellent nursing care is required to evaluate patients on a frequent and regular basis to monitor for complications. Patients with arterial lines may have excessive blood tests; in small infants this may contribute to the development of anemia.

Troubleshooting In cases of dampened waveform, obstruction or kinking of the catheter should be suspected. The catheter can be changed over a guide wire. The system must be zeroed at the level of the right atrium, and adjusted, if the bed of the patient is elevated. Pressure readings can be affected by the compliance of the connecting tubing and by air bubbles, but is not significantly affected by the catheter size. A 22 gauge or a 24 gauge angiocatheter is most frequently used. In neonates, a 3.5 French umbilical arterial catheter can be used. The technique of arterial cannulation is discussed elsewhere. A recently introduced OPTODE technology enables continuous monitoring of pH, PaO_2, and $PaCO_2$ via a sensor at the tip of intra-arterially placed angiocatheter. This is not yet widely available and calibration issues need sorting out at this point of time.

Central Venous Pressure (CVP) Monitoring

A **central venous catheter** (CVC) is required to care for many critically ill patients. A CVC provides important information regarding volume status (CVP), but it also permits the safe infusion of hypertonic solutions (parenteral nutrition, bicarbonate, calcium chloride, glucose) and vasoactive agents (epinephrine, norepinephrine, dopamine) that can produce severe peripheral soft tissue damage if they extravasate from peripheral lines into the local tissues. Rapid infusions of large volumes of fluids or blood products are also possible.

Principle A catheter in a large vessel (superior or inferior vena cava) or the right atrium will reflect pressure changes in relation to changes in the intravascular volume. Central venous pressure may be a good reflection of the preload of the right ventricle, if there are no anatomical problems (e.g. tricuspid regurgitation, stenosis) or changes in the pressure outside the vessels (e.g. intraabdominal/intrathoracic pressures). If there are no anatomical cardiac abnormalities, myocardial dysfunction or sepsis, it is possible to speculate that the preload in the right and left ventricle may be similar and that changes in CVP can reflect changes in pulmonary artery occulsive pressure (wedge pressure). To assess the, preload status, rather than using CVP as an absolute number, it is more important to observe trends of CVP after a fluid challenge or after a change in mechanical ventilator setting. After disconnecting the patient from the ventilator for a few seconds, the changes produced in CVP allow inference of how much the intrathoracic pressures might affect the preload. CVP will increase dramatically if there is pericardial tamponade, pneumothorax or fluid overload. CVP will decrease if there is hypovolemia, or severe bleeding.

The CVP catheter can also be used to draw blood. When the tip of the catheter is located in the superior vena cava, the blood gas obtained from it should correlate fairly well with mixed venous gas drawn at the level of the pulmonary artery, provided there is no intracardiac shunting. Mixed venous blood gas is an indirect indicator of the status of the oxygenation of the tissues. Simultaneous arterial and SVC gases after ventilatory and/or cardiovascular manipulations can be used to assess cardiovascular and circulatory function. Arteriovenous O_2 saturation difference is an indirect measure of cardiac output provided that oxygen consumption and extraction in the tissues is not abnormal (i.e. septic shock). In a patient with septic shock, mixed venous O_2 saturation ($ScVO_2$) will be progressively lower because tissues extract more oxygen due to increased oxygen demand, inadequate supply due to poor cardiac output as well as abnormal tissue capillary perfusion. In the same patient at a later moment, the mixed venous O_2 saturation could be high, reflecting the inability of the tissues to extract O_2 secondary to a defect in the mitochondrial function.

CVCs may be inserted from different sites; the catheter is advanced into the thoracic cavity with the tip in the inferior or superior vena cava. Sites include the femoral, subclavian, external jugular, internal jugular, antecubital, and, rarely, saphenous veins. These catheters may be inserted percutaneously or via cutdown and tunneled under the skin to reduce the risk of infection. Catheter sizes vary with the size and age of the patient. Ideally, one should attempt to insert a multilumen catheter because this provides multiple ports for the various infusions required to care for the patient. Before the procedure the patient should have ECG leads placed so that heart rate is monitored during the procedure to look for any dysrhythmias from inadvertent intracardiac placement.

The line tip should be placed at the atriocaval junction to minimize the chances of cardiac perforation and tamponade. An x-ray film ensures that the catheter is in proper position. The catheter is connected via a transducer to the monitor to enable one to evaluate the waveform and obtain a CVP. A true CVP waveform contains characteristic a, c, and v waves. The presence of these waves ensures appropriate placement in the thoracic cavity but not necessarily in the appropriate location, and therefore a chest X-ray film is required. Rarely, an intravenous dye contrast study or fluoroscopy may be needed to confirm placement, because some catheters are not radiopaque. Ultrasonic guided central venous catheterization, via images or sound (Doppler for arteries), is helpful in difficult situations. An equipment called SONOSITE (a portable mini ultrasound machine) is available for locating the vein and the artery in difficult situations.

Immediate complications of CVC include dysrhythmias, pneumothorax, hydrothorax, hemothorax, air embolism, shearing of the vessel, intravascular loss of the guide wire, bleeding, apnea, oversedation, or airway obstruction. The patient should be monitored for any of these early complications. Infection usually occurs later and is associated with longer duration of catheter placement as well as percutaneous versus tunneled catheters. Thrombosis is a concern because of the duration of the catheters and the potential for associated pulmonary embolic events. The most serious and life-threatening acute or delayed complication is cardiac tamponade. This is usually the result of an intra-atrial catheter. This problem must be immediately recognized and aggressively treated.

Cardiac Output

Cardiac output can be assessed non-invasively through echocardiography and Doppler ultrasound technique.

Principle By using the M-mode and two-dimensional (2-D) echocardiography, one can assess the dimensions of the ventricles and their changes in size in different cycles. With these measurements (left ventricular end systolic (LVES) and end diastolic (LVED) dimensions), ejection fraction (EF) and shortening fraction (SF) can be calculated. With echocardiography, it is possible to measure the aortic root diameter. If we combine this measurement and the doppler measurement with the velocity of blood flow through the aorta, it is possible to determine cardiac output. While this is a fairly adequate non-invasive technique, Swan Ganz pulmonary artery catheter thermodilution technique, although rarely used, remains the gold standard for measuring cardiac output. Now a days non-invasive cardiac output measurements are available with various gadgets mainly well tested in adult critical literature, with on going trials in pediatric patients.

NON-INVASIVE ESTIMATION OF CARDIAC OUTPUT (CO)

CO Estimation from Expired Gas (indirect Fick's Principle)

Fick's principle postulates that the blood flow through the alveoli is equal to the ratio of the uptake or elimination of a gas and the difference in concentration of the gas in the blood flowing into and out of the lungs.

All these techniques require tracheal intubation and controlled ventilation. There is a poor correlation in patients with lung diseases.

CO_2 Rebreathing Method

The concept of non-invasive CO estimation by disturbing the CO_2 transfer to the lungs in a controlled fashion has been around for more than 20 years. The alveolar CO_2 can be changed during a single breath e.g. by manipulating the ventilation or using valves to make the subject rebreath some of the CO_2 exhaled during the previous breath. These techniques were unsuitable for continuous CO monitoring because of the difficulty of non-invasively measuring mixed venous CO_2 tension. This problem was partly overcome by development of the differential Fick's principle.

Differential Fick's Principle

Rearranging the Fick's equation for the mass of CO_2 into differential form reveals that pulmonary capillary blood flow (PCBF) is proportional to the ratio of CO_2 flux from the mixed venous blood to the alveoli (VCO_2) and the change of CO_2 content of the alveolar gas ($CaCO_2$):

$$PCBF = DVCO_2/CaCO_2$$

Here paired sets of gas exchange measurements are made separated by a respiratory maneuver, usually a change in serial dead space. CO_2 elimination has been used for this purpose.

The NICO system (Novamatrix Medical System, Inc, Wallingford, CT) continuously measures airway flow, pressure and CO_2 concentration. The NICO system controls and monitors the performance of a pneumatically controlled valve assembly which consists of a rebreathing valve with large bore tubing and a combination CO_2/flow sensor.

Throughflow Technique using a Soluble Inert Gas

This technique uses continuous simultaneous measurement of gas exchange from the two lungs that are ventilated with different inspired concentrations of soluble inert measurement gas. This is expensive and cumbersome technique.

Impedance Cardiography

Thoracic Bioimpedance/Thoracic impedance cardiography (TIC) The assessment of stroke volume relies on the measurement of changes in transthoracic electrical resistivity. These changes are due to the ejection of blood into the ascending aorta with each cardiac cycle and are phasic in nature. To measure thoracic electrical impedance, an alternating current of low amplitude and high frequency is introduced and simultaneously sensed by 2 sets of electrodes placed around the neck and xiphoid process.

The base thoracic impedance reflects primarily interstitial, intracellular and alveolar fluid and has been found to correlate closely with chest radiographic findings of pulmonary, alveolar and interstitial edema. Impedance cardiography is also being investigated for use in children who are too small for placing a pulmonary artery catheter.

Status of TEB TEB is the only truly non-invasive technique, low cost, facing vigorous investigation and appears most promising of all.

Whole body impedance cardiography (Tishchenko-1973) Here electrodes are attached to both the wrists and ankles (an advantage over TIC in perioperative cardiac patients). This technique has been found to measure CO accurately in different clinical settings, correlate well with thermodilution technique and unlike TIC, atrial fibrillation does not impair the accuracy of CO estimation.

Limitations awake and moving patients, hypothermia [minimal error Body mass index (BMI)], inaccurate Stroke volume (SV) estimation if incorrect Hematocrit (HCT) or BMI values are used in SV calculation.

Endotracheal tube bioimpedance Phasic impedance flux at the distal end of endotracheal is used to estimate CO. This technique is still in experimental stage.

Ambulatory Impedance Cardiography

A wearable, ambulatory impedance monitor (AIM) has been developed to permit impedance cardiographic measurements while patients and volunteers engage in normal daily activities. AIM holds the potential for providing insights into previously unexplored aspects of cardiovascular control during the activities of daily living.

Pulse Contour Analysis

Pulse contour analysis gives us a host of measured and derived parameters, heart rate, rhythm, systolic, diastolic and mean blood pressures, stroke volume, vessel wall compliance, CO, SVV, pulse pressure variation (PPV), central capacitance tone and arterial tone. The vessel wall compliance is a predictor of underlying or potential atherosclerosis and arterial tone is a major determinant of cardiovascular performance. Left ventricular SVV in response to positive pressure ventilation, and also PPV and SPV as surrogates of SVV are currently undergoing thorough scrutiny as reliable and objective markers of fluid responsiveness, with mixed result.

Non-invasive Non-invasive application of this technique is still under investigation in various non surgical, but acute settings and holds great promise.

Invasive

PICCO System (Figs 7.3 and 7.4)

The PICCO system uses transpulmonary thermodilution to calibrate a pulse contour analysis algorithm of the arterial waveform. The morphology of the aortic waveform is analysed via a femoral artery catheter, and an attempt to delineate the ejection systolic area (i.e pressure waveform between the start of ventricular ejection and the dichrotic notch) is made by a computer algorithm. Once the algorithm is calibrated, changes in the ejection systolic area and the heart rate are displayed as changes in CO.

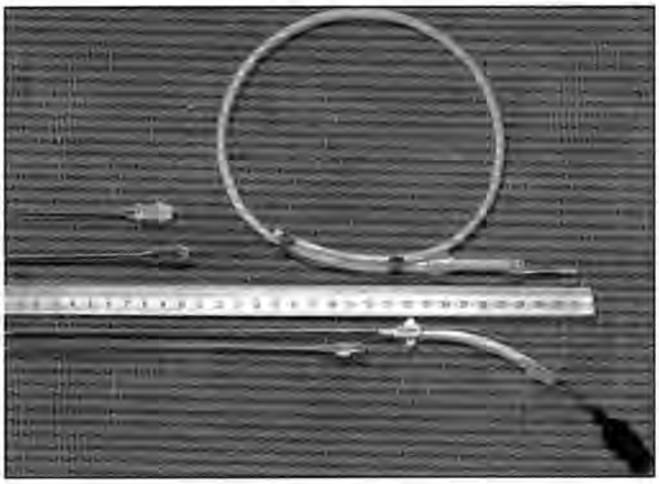
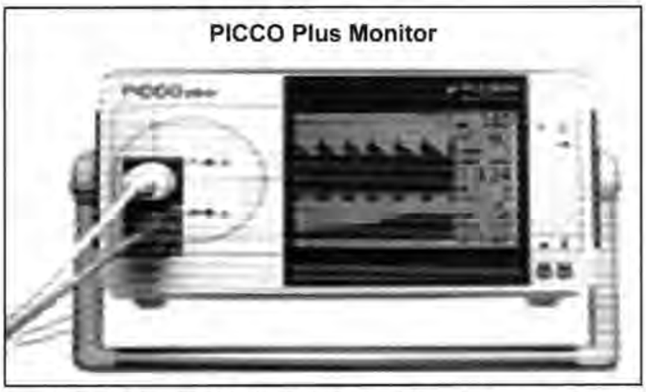


Fig. 7.3: PICCO (Partially invasive pulse contour CO monitoring) (*For color version see Plate 2*)



PICCO Plus Monitor

Fig. 7.4: Partially invasive cardiac output monitor (*For color version see Plate 2*)

PICCO is a physiological monitor providing less invasive continuous arterial pulse contour CO, preload and extravascular lung water monitoring. A variable correlation with thermodilution CO measurement has been described.

Clinical experience of this system is developing but arrhythmias, unusual waveform morphology, and certain vasoactive drugs can produce errors in the estimation. The interval between calibrations has yet to be determined but may have to be relatively frequent in unstable patients PICCO also provides additional information like intrathoracic blood volume, global end diastolic volume, contractility index and extravascular lung water.

Lithium Dilution CO

Lithium is a good alternative marker for the indicator dilution method of estimating CO because it is safe, non-toxic in small doses, and easy to measure using an ion-selective electrode. There is no significant first pass loss from the circulation and it is rapidly redistributed.

Studies have shown that pulse contour measurements of CO are reliable for at least 8 hour after cardiac surgery despite the potential inherent fluctuations in the arterial pressure waveform caused by temperature changes, use of vasopressors, inotropes or vasodilators, or use of the arterial line for blood sampling after a single calibration.

Edwards

The *Vigileo* monitor continuously computes patient specific stroke volume from, arterial pressure analysis, inputs of age, gender, height and weight determine patient-specific vascular compliance and dynamic changes in the vasculature (peripheral resistance and vascular tone), which affect arterial pressure, are measured and compensated for.

This APCO algorithm provides a reliable, minimally invasive method for measuring CO that requires neither dilution nor CO reference for calibration. It shows strong correlation and minimal bias with both traditional intermittent bolus thermodilution and continuous cardiac output over a wide range of values.

In Adults Non-invasive monitoring will not replace invasive monitoring, in immediate future, which currently reflects the "gold standard" and is used to standardize non-invasive monitoring systems. However, the development of an applicable model for non-invasive monitoring for a wider array of patients may provide opportunity for earlier prognostication and intervention i.e. pre event rather than post event management. If response to early intervention, as indicated by non-invasive monitoring methods, is appropriate then less invasive monitoring can be continued. If the response is not appropriate, then invasive monitoring may be warranted. Also such simple non-invasive techniques with their inherent advantages of cost effectiveness, ease of use and acceptable accuracy may have a major role to play in peripheral ill equipped hospitals in the developing countries which may not have resources and expertise for invasive hemodynamic monitoring techniques.

Echocardiographic CO Estimation (Fig. 7.7) is done either by using a Doppler flow probe or real time imaging of changes in LV size. Some echocardiographic machines can automatically measure and calculate cardiac output (Automatic CO measurement) and some have automatic border detection, permitting continuous area changes measurement to give stroke volume.

TEE (Trans Esophageal Echocardiography)

Clinical trials support TEE as a reliable alternative for intraoperative CO measurement and for its ability to track serial changes throughout the surgical procedure.

Doppler Measurement of Cardiac Output

The technique is to use back scattering of ultra sonic waves to measure the Doppler shift generated by the blood moving through the arteries. What actually gets measured is the average velocity of blood flow inside the space that the sound beam crosses. In this method the velocity time integral (VTI) of blood, the cross section area of the conduit across which VTI is obtained and heart rate is used to calculate the CO. In most of the currently available methods of determining CO, anatomical or functional abnormalities of the heart or great vessels are likely to result in erroneous readings. Particularly problematic anatomical abnormalities are valvular regurgitations and anatomical shunts. Arrhythmias also cause erratic estimation of cardiac output.

External probe Ultra Sonic Cardiac output Monitor (USCOM) is a commercially available device of this type. USCOM has a non-imaging transthoracic probe and uses continuous wave (CW) doppler signals to obtain a velocity time integral (VTI) at ascending aorta or pulmonary artery. The cross section area (XSA) of the vessel is predicted by a height based nomogram, which is incorporated in the USCOM software. Stroke volume (SV) is measured by XSA x VTI and CO by SV x Heart Rate (HR). USCOM is non-invasive, portable, less expensive, does not require skilled operator, has short learning curve and appears to be most promising. The drawbacks are use of nomogram to estimate cross section area of vessel and not enough clinical validation as of now. In a recently concluded study at our center, we found that USCOM CO estimation in post op pump coronary artery bypass (OPCAB) patients correlated quite well with thermodilution CO (Fig. 7.5).

Transesophageal Probe (TECO)

A non-disposable probe is placed into the esophagus. Till date not many studies have described clinical use and accuracy of TECO. Moreover, the esophageal probe does not measure the part of the CO given to the head and upper extremities (a limitation vis a vis supra sternal probe). We found poor correlation between TECO CO estimation and thermodilution CO in post OPCAB patients and correct positioning of the probe was also a frequent problem.

Transtracheal Doppler The equipment consists of 5 mm ultrasonic transducer bonded to the distal end of an endotracheal tube. The theoretical advantages of this method over transesophageal approach are that measurement of blood flow is in ascending aorta (proximal to arch vessels) which allows for a more constant anatomical relationship between trachea and ascending aorta.

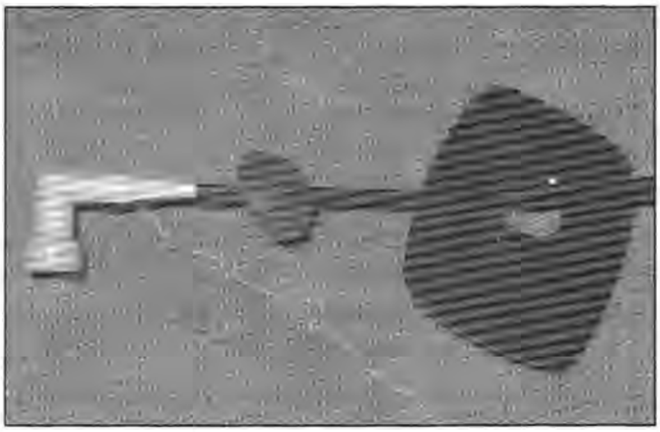


Fig. 7.5: Doppler technique of cardiac output estimation (USOM CO) temperature monitors *(For color version see Plate 3)*

Disadvantages

- Damage to airway structure.
- Frequent manipulation for probe placemen required.

Monitoring of Temperature:

Principle There are multiple devices to measur temperature: glass-mercury thermometers, electronic rectal and oral thermometers, and infrare thermometers. Tympanic thermometer using infrared thermography technology is relatively new. Th advantage of this technique in relation to others i mainly simplicity and rapidity. It seems that it i fairly reflective of brain temperature, which can b advantageous in treating hypothermic patients. A extensive review and comparison of these technique has been published.

There are different types of equipments fo continuous temperature monitoring at the level o skin, nasopharynx, esophagus, rectum and urinary bladder. In pediatric intensive care continuous temperature monitoring is commonly done by rectal probe with a temperature sensor at its tip. Children respond to decrease in perfusion with increased vasoconstriction and this produces a decrease in the temperature of the extremities. In some European countries, continuous monitoring of temperature of the great toe is being used as monitor of the circulatory status. The difference in temperature of the core and extremities may also be an indicator of the circulatory status, but its use in a clinical settings has not yet been standardized.

RESPIRATORY MONITORING

Pulse Oximetry

This is a technology that has proven its efficacy in the pediatric intensive care unit as well as other intensive care units. Pulse oximetry is the standard for non-invasive bedside oxygenation monitoring. Pulse oximetry can be used in patients of all ages and does not usually cause tissue damage. Its accuracy is dependent on adequate tissue perfusion; its utility is limited in patients with significant vasoconstriction and poor peripheral perfusion. Pulse oximetry measures oxygen saturation, not the partial pressure of a gas.

This is important in interpreting the significance of the value obtained. Normally, arterial oxygen saturation is 95% or more (except in patients with cyanotic congenital heart lesions). Although pulse oximetry does not provide PaO_2, it provides just as good if not better information regarding real-time oxygen saturation. It permits the rapid assessment of oxygenation of a critically ill patient. It requires little, if any, warm-up time and is extremely portable, enabling one to assess oxygenation of patients not only in the PICU but also during transport , during procedures that require conscious sedation, and in various non-ICU settings, such as the emergency department or office.

The information is extremely reliable and relatively inexpensive compared with blood gas analysis. Pulse oximetry does not provide direct measurements of carbon dioxide tension, acid-base status, or bicarbonate levels.

Principle It is a combination of two technologies: Plethysmography and Spectrometry that provides, non-invasive measurements of pulse rate and hemoglobin saturation respectively. It functions by positioning a pulsating arterial vascular bed (fingertip, or ear lobe) between a two-wavelength light source LED (light-emitting diode) and a photodetector. The monitors ignore the continuous absorption of light by tissue, venous, capillary, and nonpulsatile arterial blood performing an analysis of the light absorption of pulsatile arterial blood only. Blood is composed of two light absorbers, oxyhemoglobin and deoxygenated hemoglobin. Each retains different amounts of the two-wavelengths of light utilized (red and infrared). Analysis of this absorption provides a ratio of these hemoglobins. A pulse oximeter measures the functional saturation of the hemoglobin (per cent of the oxyhemoglobin in relation to the sum of oxyhemoglobin and deoxygenated hemoglobins. It does not take into account the presence of abnormal hemoglobins such as carboxyhemoglobin, or the methemoglobin. Fractional oxyhemoglobin saturation measured by the cooximeter gives a true oxyhemoglobin saturation.

$$\text{Functional Saturation} = \frac{O_2Hb}{O_2Hb + Hb}$$

$$\text{Fractional saturation} = \frac{O_2Hb}{O_2Hb + Hb + COHb + Met\,Hb}$$

The pulse oximeter provides an accurate measurement of the arterial oxygen saturation in the range of 60-99 percent and is not significantly affected by fetal Hgb, bilirubin, or tissue thickness. It is unable to work when there is decreased vascular perfusion (hypotension, hypovolemia, hypothermia, infusion of vasoconstrictive agents, shock, inflated BP cuff, or tourniquet). Light may interfere with the photodetector. In the presence of abnormal hemoglobins, the values displayed are unreliable as explained before. Intravenous dye injection (methylene blue) can cause false readings. Nail polish can affect the accuracy of the oxygen saturation. In a patient with carbon monoxide poisoning, pulse oximeter saturation (functional) may be 100 percent even though percentage of circulating carboxyhemoglobin may be 15 per cent. In such a situation, only a cooximeter can measure the true saturation to be 85 percent (fractional saturation). It is, therefore, important to bear this fact in mind that pulse oximeter reading may be falsely elevated since it ignores carboxyhemoglobin, and measures only oxyhemoglobin and deoxyhemoglobin ratio in the pulsatile blood.

Troubleshooting LED's and photodetector (PROBE) need to be positioned in front of each other around an ear lobe or a large digit secured with a piece of tape. Sensor should be covered with microfoam tape. It should not be placed on the same arm as the BP cuff. Light interference or motion artefacts prolong the average time of measurements before displaying a reading.

Blood Gas Monitoring

The monitoring requirements for patients who require significant respiratory support include blood gas determination, either from arterial or, less frequently, capillary and venous blood gases. Arterial blood gas sampling requires special technique similar to inserting an arterial line. Capillary gases usually involve the use of the infant's heel. It must be warmed to "arterialize" the blood. In the laboratory a blood gas analyzer measures the partial pressures of oxygen and carbon dioxide and the pH; the bicarbonate is usually calculated from the pH and PCO_2. The pH and $PaCO_2$ from a capillary or venous sample should closely resemble the arterial blood gas sample. However, the capillary PO_2 does not correlate well with the PaO_2; and in circumstances in which peripheral blood flow is adversely affected all other parameters obtained from capillary blood gases may not correlate. Capillary and venous blood gas sampling have significant limitations.ABG interpretation is a separate subject,that will not be discussed here.

Intermittent blood gas sampling is labor intensive and expensive. It does provide the most reliable assessment of acid-base and ventilation-oxygenation status in the critically ill patient. When the patient's clinical status requires both continuous blood pressure monitoring and frequent assessments of respiratory status, an indwelling arterial line is indicated. Devices can provide continuous pH, $PaCO_2$, and PaO_2 when the monitoring catheter is placed in an artery; blood flows from the catheter into a closed-loop system passing the blood gas electrodes. The data are obtained in a continuous manner or intermittently. These devices are expensive and require blood vessels of sufficient size to permit the insertion of a large catheter (at least 20 gauge). These devices are useful when placed in central venous lines and used in conjunction with pulse oximetry; this combination demonstrates good correlation of venous pH, with arterial pH and venous PCO_2 with arterial $PaCO_2$.

Point of care testing in the PICU and neonatal ICU (NICU) is more expensive yet more expedient and provides valuable information in minutes and at the bedside. Point of care testing may be accomplished with a handheld device that is also useful in the transport environment, in areas where the patient is not in the PICU but must have blood gas analysis performed, such as radiographic imaging sites, or when the patient's condition is so unstable that an instantaneous analysis is required. These simple devices may perform a number of other analyses, such as measuring serum electrolytes, glucose, creatinine, urea, ionized calcium, and hematocrit.

A variety of non-invasive devices and monitors have improved the care of critically ill children. Portable I-STAT and IRMA blood gas and electrolyte analyses are available in India.

Capnography

End-tidal CO_2 ($ETCO_2$) analysis (capnography) measures the Pco_2 in the exhaled gas. This technique is used in patients who are intubated and have minimal lung disease without significant intrapulmonary shunting. Capnography is based on the principle that the highest concentration of CO_2 sampled in the respiratory circuit represents the alveolar CO_2 concentration, which should also be close to the arterial ($PaCO_2$) concentration. Gas is constantly monitored from a side port to the connector from the ventilator to the endotracheal tube. A small amount of gas is diverted from the respiratory circuit and analyzed in a spectrophotometer for Pco_2 determination. The removal of small amounts of respiratory gas must be accounted for when calculating delivered and exhaled tidal volumes.

When interpreting $ETCO_2$ results, one needs to evaluate the graphic picture of the exhalation capnographic image to ensure that the alveolar plateau and peak are achieved. Patients who have significant intrapulmonary shunts or are spontaneously breathing may not produce an acceptable capnographic trace, and thus invalidate end-tidal CO_2 monitoring. This device permits trending and the potential for weaning of patients from mechanical ventilation; it does not replace blood gas analysis.

Capnography can also determine if one has intubated the trachea and is useful in emergent intubations. Using an analyzer that changes color on exposure to levels of CO_2 enables one to differentiate between an esophageal and tracheal intubation. The CO_2 concentration in the stomach is very low, approaching atmospheric levels of close to zero, whereas that in the lungs is markedly higher. With cardiopulmonary arrest and absent pulmonary blood flow, $ETCO_2$ will also be undetectable. Indeed, successful reestablishment of the circulation can also be assessed by an elevation of $ETCO_2$.

Arterial – end tidal CO gradient [(a – ET) pCO_2]

In normal lungs, this difference is between 2 – 5 mm Hg and is an indicator of the dead space. In conditions in which there is an increase in the total dead space, such as severe parenchymal lung disease or decreased blood flow to the lungs, the measured ET CO_2 will decrease and there will be an increase in the a-ET CO_2 gradient. The magnitude of the gradient corresponds to disease severity and repeated measurements can be used to assess disease progression.

End tidal CO_2 measurement is an extremely useful non invasive measurement. It provides much more information that just an approximation of the arterial CO_2. Newer technology allows the use of lightweight, portable instruments both in hospital and during transportation. Disposable CO_2 detectors allow secondary confirmation of endotracheal intubation.

NEUROLOGIC MONITORING

The Glasgow coma scale (GCS) (Table 7.1) is the most useful clinical index to monitor conscious status. It is simple to perform and is oriented to measure arousability, mediation, and functional integrity of the major central nervous system (CNS) pathways. It takes into account eye opening, best motor response and best verbal response. It should be performed consecutively. The scores range from 3 to 15. It can be adapted for children and, in patients with head injury, it may have a prognostic value.' Score less than nine is suggestive of significant coma or severe head injury; there is loss of adequate protective airway reflexes and most probably a loss of the autoregulation of the cerebral blood flow. Therefore, patients with a GCS of less than nine should be intubated and mechanically ventilated with additional precautionary measures to prevent increased intracranial pressure (ICP). Depending on the etiology of the insult, GCS may determine which patients are at a high-risk for secondary brain injury and who may be candidates for invasive ICP monitoring.

Invasive neurologic monitoring involves ICP monitoring and jugular bulb catheterization.

Jugular bulb monitoring enables one to obtain continuous oxygen saturation ($JSaO_2$) measurements using an indwelling fiberoptic catheter placed in the jugular vein and advanced cephalad to the level of the jugular bulb. The values obtained correlate with the jugular PaO_2 content and do not require blood sampling for actual determination of the oxygen saturations. The jugular bulb is located at the base of the skull and just outside the jugular foramen. It is the point of exit of the blood draining most of the cerebral hemispheres. The clinician is provided with information that enables one to determine how well the injured brain is utilizing oxygen. By knowing the saturations of oxygen in both the systemic arterial and jugular vein, one is able to calculate the arteriojugular difference for oxygen ($AJDO_2$). This is normally 4–9 mg/dL. Levels below this indicate cerebral hyperemia, and the clinician may select therapies designed to decrease cerebral blood flow. Levels greater than 10 mg/dL may indicate ischemia and necessitate further tests to determine the extent of the brain injury. It is hoped that using the values obtained from ICP, $AJDO_2$, and cerebral blood flow, one may alter therapy to improve outcome. This modality is used in tertiary level neurointensive case units.

Table 7.1: Glasgow Coma Score

Eye opening	No response	1
	Response to pain	2
	Response to voice	3
	Spontaneously	4
Verbal response	No response	1
	Incomprehensible sounds	2
	Inappropriate words	3
	Disoriented conversation	4
	Oriented and appropriate	5
Motor response	No response	1
	Decerebrate posturing	2
	Decorticate	3
	Flexion withdrawl	4
	Localizes pain	5
	Obeys commands	6
	Total Score	**3-15**

Intracranial Pressure (ICP) Monitoring (Fig. 7.6)

Principle In an infant before the closure of fontanels, if there is a situation of raised intracranial pressure, it first leads to a bulging fontanel, followed by gradual enlargement of head, as seen in patients with progressive hydrocephalus. However, after closure of fontanels, the skull is rigid (non-distensible). Therefore, any increase in the mass inside the skull

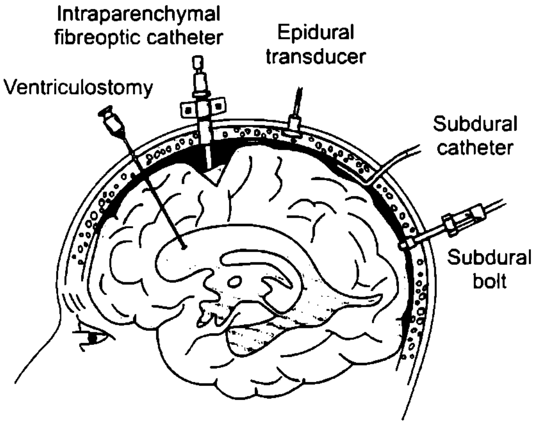


Fig. 7.6: Various devices to monitor ICP

(brain, cerebrospinal fluid, or blood) will produce an increase in ICP (Munroe Kelly doctrine). After a critical level is exceeded, increases in ICP will produce damage to the brain by compressing it or by affecting the blood supply. The indication for ICP monitoring includes any acute neurologic deterioration where elevated ICP may produce further injury to the patient. Usually, acute traumatic events with a GCS less than 8 will require a monitoring device inserted either in the operating room or at the bedside in the PICU. The type of device and how it is inserted is usually the responsibility of the neurosurgeon placing the device (Fig. 7.6). Ventriculostomy as well as intraparenchymal, subdural, or subarchnoid placement of catheters can be used. All but the intraparenchymal catheters are connected to the transducer via a fluid-filled tubing device. The ventriculostomy and the intraparenchymal fiberoptic devices are the most reliable and most used devices for monitoring ICP. A ventricular catheter allows one to not only measure ICP but also remove fluid if necessary, thereby providing a therapeutic option.

The intraparenchymal fiberoptic system provides for a very reliable method of ICP measurements, but does not permit the removal of cerebrospinal fluid (CSF). It is not a fluidfilled system but is easy to use.

The device is connected to a transducer and then to the monitor. A waveform with a numeric value is produced. The ICP should be less than 20cm H_2O. When monitoring ICP, it is imperative that the systemic arterial blood pressure be determined simultaneously. The difference between the mean arterial pressure and the ICP is the cerebral perfusion pressure. This should be more than 50 cm in older patients and slightly less in younger children. The complications associated with ICP monitoring include bleeding (check coagulation factors before insertion), infection if left in for more than 5 days, injury to the brain parenchyma (usually only intraventricular catheters), and CSF leak.

So, in summary Three types of techniques are utilized to monitor ICP. The oldest one is the direct placement of a catheter into the ventricular system. This is the gold standard, but has greater risk of infection and is difficult to perform if ventricles are not dilated. Its major advantage is that CSF can be drained through this system to decrease ICP. The same principle can be used by placing a catheter in the epidural space (epidural catheter), but there are multiple sources of mistake or misinterpretation with it. The second system is a hollow bolt that is screwed into the skull until it reaches the subarachnoid/ subdural space (Richmond bolt). One of the problems with this system is that the bolts are prone to be inadvertently obstructed by brain tissue and give false readings. The system that is becoming more popular is a fiberoptics probe which can be placed in the brain (intraparenchymal), inside the ventricles, or in the subdural space (Camino Laboratories, San Diego, CA, USA). This device is accurate, and does not need recalibration, and is usually not affected by problems of obstruction.

ICP monitoring is particularly important for those patients who have lost the capability of autoregulating brain blood flow (e.g. severe head trauma). In this case, the cerebral perfusion pressure (CPP) is going to be directly dependent on the difference between mean arterial pressure and the intracranial pressure. When CPP is less than 40 mmHg, low cerebral perfusion can be expected. Aim should be to maintain CPP at least above 50 to 60 mmHg depending upon the age of the child. It is important to remember that MAP is measured at the level of the right atrium, but the driving pressure for CPP is the MAP at the level of the carotid artery entering the brain. Therefore, if the head is elevated above the level of the right atrium (where the MAP is measured), the height difference should be subtracted from the measured MAP (1 cm = 0.7

mmHg). This type of monitoring is helpful when there are intracranial masses, and for the monitoring of ICP secondary to vasogenic edema (e.g. meningitis). The value of using an ICP monitor after cytotoxic edema (e.g. near drowning, hypoxic encephalopathy) is highly controversial. A newer method currently being tested, use a transducer placed at the level of the anterior fontanel reflective of ICP. This technology needs precise calibration, familiarization with the equipment, and an open fontanel.

Electroencephalography

Electroencephalography (EEG) and evoked potentials (EP) testing can be used as a supplement to detailed neurologic examination. Continuous monitoring is particularly useful in mechanically ventilated patients who are on muscle relaxants. EEG and EP can also provide important diagnostic and prognostic information.

EEG and somatosensory evoked potentials (SSEPs) change predictably with cerebral ischemia, and recognition of these changes may allow intervention prior to frank tissue infarction. Additional roles include identification of subclinical or nonconvulsive seizures, identification of metabolic coma; and identification of compression of neural tracts due to expanding hematomas, edematous tissue, or hydrocephalus. The early identification of ischemia or significant edema allows for ICU intervention and minute-to-minute evaluation of response to therapeutic intervention.

Electroencephalography records ongoing summated electrical activity produced by neurons in the cerebral cortex.

EEG can identify cortical abnormalities (often before CT changes are evident), it cannot reliably identify sub-cortical disease. Specific EEG patterns can be used to identify ischemic changes and predict severity of injury.

EEG The EEG has a diagnostic as well as prognostic role in coma. Typical EEG findings in some conditions causing coma are shown in Table 7.2.

EEG patterns of Burst suppression, monorhythmical alpha-like activity, electro-cerebral silence or very low amplitude, and monotonous 0.5-3 Hz high voltage activity have been associated with poor outcome. EEG findings of poor outcome do not always correlate with the clinical assessment of deep coma. The appearance of sleep spindles is indicative of a good prognosis, even in the presence of delta waves.

Table 7.2: EEG findings in certain conditions causing coma

EEG findings	*Interpretation*
*High voltage focal slow waves	Underlying supratentorial lesion
*Periodic lateralized epileptiform discharges (PLEDS)	Herpes encephalitis
Paroxysmal seizure discharges	Status epilepticus
Slowing of Alpha-rhythm	Metabolic coma
Progressing to diffuse slowing	Hepatic or other
Triphasic paroxysmal waves 2-4 Hz/sec bilaterally	Metabolic coma

Evoked potentials are produced by stimulating a sensory system and recording the electrical activity that follows. EPs can follow somatosensory auditory stimulation brainstem auditory evoked responses (BAER), or visual stimulation (visual EP). The target EP activity occurs at a reproducible time after the stimulus. All EP responses are characterized and defined by latency and amplitude criteria. These responses occur sequentially.

Amplitude of EEG activity or the amplitude of EP responses, are of limited usefulness as strict criteria for defining disease because of high variability among normal subjects. The large range of patient-to-patient variability becomes less of a concern when EEG or EP are used for continuous monitoring in the PICU. An important premise for such monitoring is that the amplitude and latency of responses for a single patient are expected to remain relatively constant over short periods of time (hours to day), provided that those areas of the nervous system responsible for the responses are unaffected by disease. If the data change significantly, then a significant clinical change (for better or worse) is expected.

The identification of seizures, especially non-convulsive seizures (NCSE), is a clear benefit of continuous EEG monitoring. NCSE can manifest as coma, and signs of seizure (nystagmus, or twitching of facial or upper limb muscles) may be absent or subtle. Outcomes after PICU stays are worse if NCSE occurs, especially if the NCSE is prolonged or the diagnosis is delayed. It is expected, but not proven, that early recognition of NCSE would reduce the chance of further cerebral damage. Continuous EEG is more capable of distinguishing NCSE patterns from coma patterns in toxic/metabolic coma than in routine, intermittent EEG.

In summary, EEG and EP monitoring can be powerful tools for identifying neurophysiologic changes.

Transcranial Doppler Sonography

Transcranial Doppler sonography (TCD) is currently the most versatile and widely available quantitative technique of assessing CBF. TCD can be performed quickly at the bedside with minimal interference with patient care, and it can be repeated as often as necessary. If desired, the TCD probe can be held in position by a headband for continuous monitoring. Analyzing the cerebral blood flow velocity (CBFV), resistance index, or pulsatility index of intracranial and extracranial arteries, and by performing arterial compression tests when appropriate, one can monitor the development of vasospasm, the pattern of collateral circulation through the Circle of Willis, or the development of brain death.

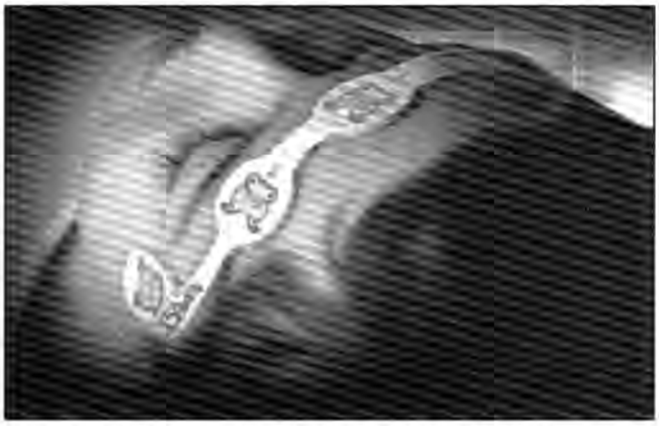
Newer Neurological Monitoring Techniques

Some of the newer techniques such as microdialysis, NMR spectroscopy, Infrared oximetry have been used in PICUs in the western countries not yet universally applicable in Indian context.

Monitoring of a mechanically ventilated patient receiving continuous sedation and neuromuscular blocking agents is discussed in the chapter on sedation in the PICU.

The Bispectral Index (BIS) can be used to monitor the neurologic status of both sedated and unsedated critically ill patients. Leads(comes as a strip of tape with metal leads) are placed on the forehead of the patient and connected to the BIS module on the monitor.

BIS is a statistically derived variable that provides information about the interaction of brain cortical and subcortical regions. The BIS score ranges from



Brain monitoring technology for objective sedation assessment of pediatric patients in the ICU

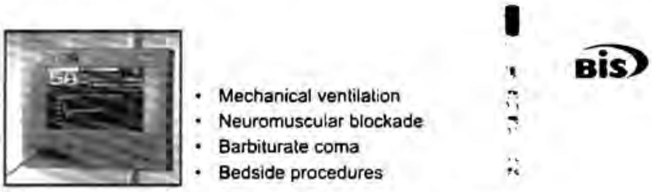


Fig. 7.7: BIS scale in use with monitor (*For color version see Plate 3*)

0–100 and is a reliable index of the state of consciousness in normal subjects. Scores more than 95 indicate full consciousness. Of sedated patients, 95% are unconscious if the BIS score is 50. BIS correlates with the depth of sedation of patients who require mechanical ventilation and sedation after surgery or medical illness (Fig. 7.7). BIS has been proposed as a guide to prevent oversedation in the critically ill. Unfortunately, the BIS score may be complicated if the EEG also reflects changes in the neurologic status of the patient that are caused by the illness itself.

So its use is mainly for patients without a neurological illness who are sedated due to being on a mechanical ventilator. There are some preliminary reports on its use in the neonates (see BIS references 42-45).

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CHAPTER

8

Capnography

Praveen Khilnar

Carbon dioxide is produced during cellular metabolism, circulated to the pulmonary alveolar capillaries via right ventricle and pulmonary artery, diffusing out to the alveolar space, expired at the end of tidal breathing. A process of measuring it is known as *Capnometry*.

A graphic display of end-tidal CO_2 ($ETCO_2$) concentration analysed in the expired air is known as Capnography.

Physiological Significance

Three factors determine $ETCO_2$:

- **End-tidal CO_2 values are related to adequacy of ventilation (in hyperventilation end-tidal CO_2 goes down, hypoventilation leading to increased $ETCO_2$).**
- End-tidal CO_2 is directly proportional to cardiac out put reaching the lungs. The less the cardiac output the lesser the end-tidal CO_2 (in cardiac arrest,pulmonary embolism end-tidal CO_2 drops). If minute ventilation and cardiac output are kept constant than end-tidal CO_2 reflects the amount of CO_2 produced (hypermetabolism, sepsis, malignant hyper-pyrexia).

CO_2 transport

- CO_2 produced by tissues diffuses to blood (Fig. 8.1)
- 5-10 percent physically dissolved
- 20-30 percent protein bound as carbamino compounds
- 60-70 percent carried as HCO_3 to lungs
- In alveoli CO_2 diffuses out to be expired.

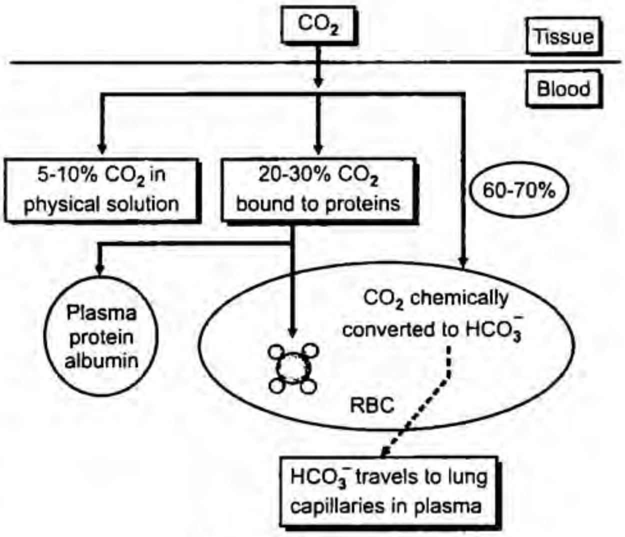
CO₂
Tissue
Blood
5-10% CO₂ in physical solution
20-30% CO₂ bound to proteins
60-70%
Plasma protein albumin
CO₂ chemically converted to HCO₃⁻
RBC
HCO₃⁻ travels to lung capillaries in plasma

Fig. 8.1: CO_2 transport

Measurement of CO_2 can be done by

- Mass spectrometry
- Infrared spectrometry
- Photoacoustic spectrometry
- Raman spectrometry
- Ferum detector

Infrared Spectrometry

- Infrared spectrometry is the most commonly usec method. It compares the amount of infrared ligh absorbed by a sample of patient gas to the amoun of light absorbed in a chamber containing knowı concentration of carbon-dioxide.

Factors affecting infrared spectroscopic measurements:

- Temperature
- Pressure
- Presence of other gases
- Contamination of gas chamber
- Calibration
- Collision broading

Methods of ETCO$_2$ Sampling (Fig. 8.2)

Main Stream Sampling

CO$_2$ sensor is placed in the patients airway attached to an adapter. Its main disadvantages include inability to monitor nonintubated patient and the adapter carrying CO$_2$ sensor may be heavy, adds significant dead space and moisture and secretions in exhaled gases may affect calibration.

Side Steam Sampling

Respiratory gases are continuously aspirated from an adapter placed at the patients airway and transported to the optical bench via sampling tube.

Main advantages are lack of additional weight on the airway and no deadspace. Main disadvantages include water and mucus obstructing the sampling tube, lag time in collection and measurement.

If fresh gas flow rates are too high, inspired gases may be aspirated into the sampling tube giving falsely low ETCO$_2$ values.

Alveolar Arterial CO$_2$ Gradient (A-aDCO$_2$) (Normally 2-3 mmHg)

The Difference can be widened if alveolar emptying is incomplete, poor sampling, or ventilation perfusion abnormalities.

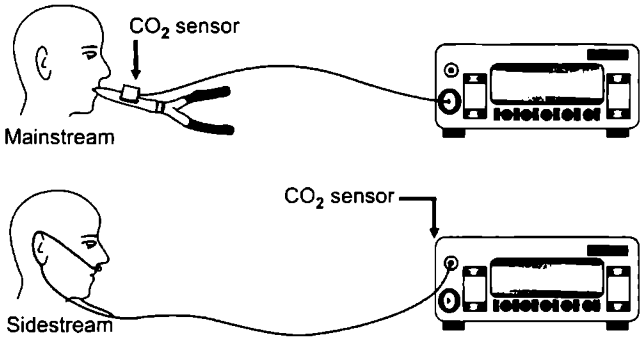

Fig. 8.2

- Dead space = high ventilation, no perfusion (high VQ ratio)
- Caused by pulmonary embolism, cardiac arrest, systemic hypovolemia, alveolar hyperinflation compressing capillaries. A—a difference is widened.

Normal VQ = 0.8 4parts ventilation, 5 parts perfusion

- Shunt = (low VQ ratio) High perfusion, no ventilation
- Atelectasis, mucus plugging, right mainstem bronchial intubation. Aa difference is usually not wide due to compensation by rapid diffusion of CO$_2$ in ventilated areas.

Normal ETCO$_2$ Waveform (Fig. 8.3)

Normal waveform displays wave from point A to point E

A. Zero baseline
B. A rapid sharp rise
C. An alveolar plateau
D. A well defined end-tidal point
E. A rapid sharp downstroke.

A-B : Exhalation of CO$_2$ free gas from dead space.
B-C Combination of dead space and alveolar gas.
C-D : Exhalation of mostly alveolar gas (alveolar plateau).
D "End-tidal" point-CO$_2$ exhalation at maximum point.
D-E Inhalation of CO$_2$ free gas.

Abnormal Waveforms: Various Abnormal

Wave forms and their clinical significance is shown (Figs 8.4 to 8.11):

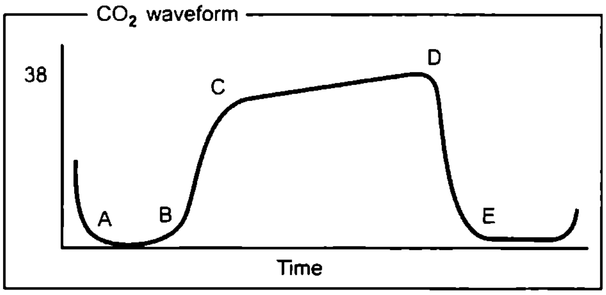

Fig. 8.3

Sudden loss of $ETCO_2$ to zero or near zero (Fig. 8.4)

- Esophageal intubation
- Complete airway disconnection from ventilator
- Ventilator malfunction
- Totally obstructed /kinked endotracheal tube.

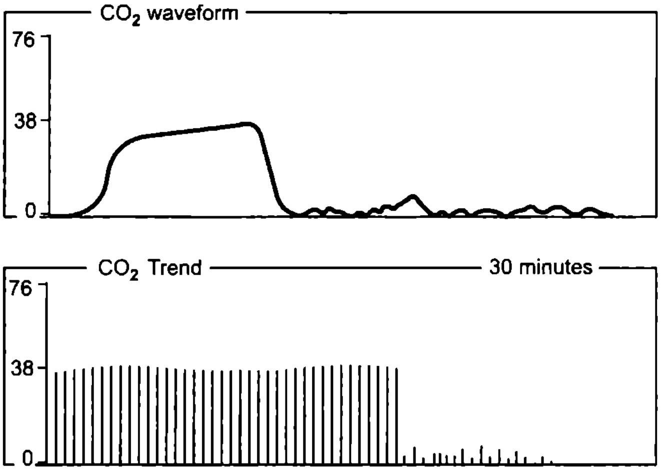

Fig. 8.4

Exponential Decrease in $ETCO_2$ (Fig. 8.5)

- Sudden hypotension, massive blood loss
- Circulatory arrest with continued pulmonary ventilation
- Pulmonary embolism
- Cardiopulmonary bypass

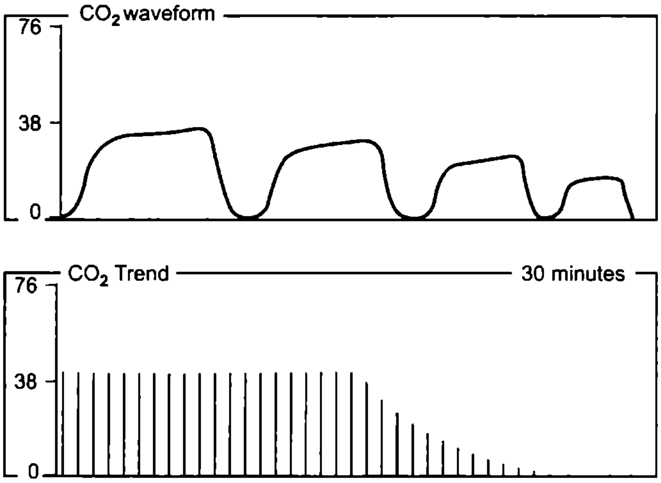

Fig. 8.5

Gradual increase in $ETCO_2$ (Fig. 8.6)

- Rising body temperature
- Hypoventilation
- Partial airway obstruction, as in foreign body aspiration.

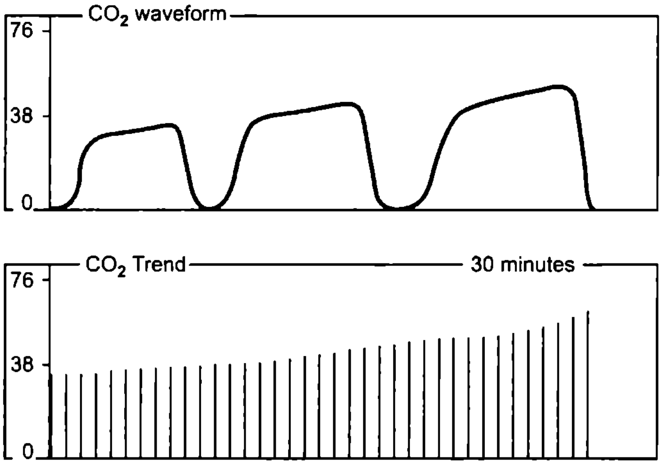

Fig. 8.6

Sudden drop in $ETCO_2$ to low but non-zero value (Fig. 8.7)

- Leak in the airway
- Partial disconnect in the ventilator circuit
- Partial airway obstruction caused by secretions
- Endotracheal tube in hypopharynx.

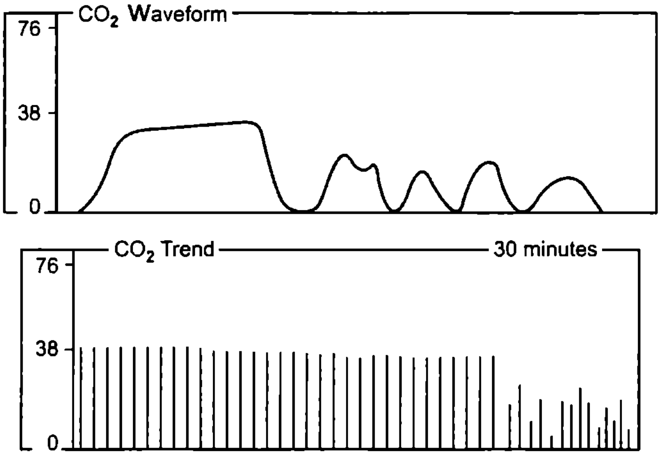

Fig. 8.7

Sustained low $ETCO_2$ with a good plateau (Fig. 8.8)

- Pneumonia
- Hyperventilation
- Hypovolemia.

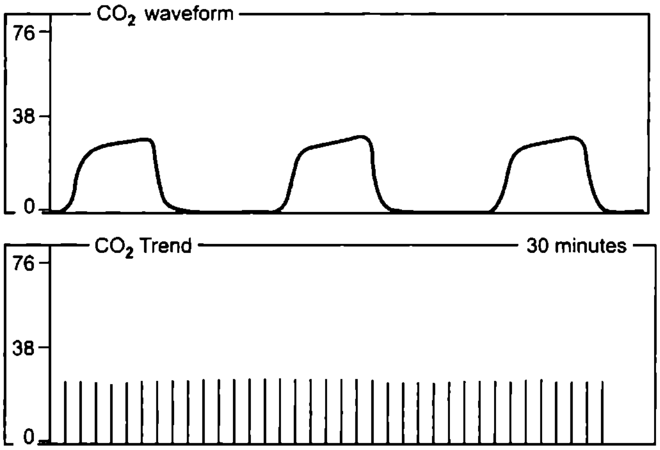

Fig. 8.8

Cleft in alveolar plateau (Fig. 8.9)

- Partial recovery from neuromuscular blockade.

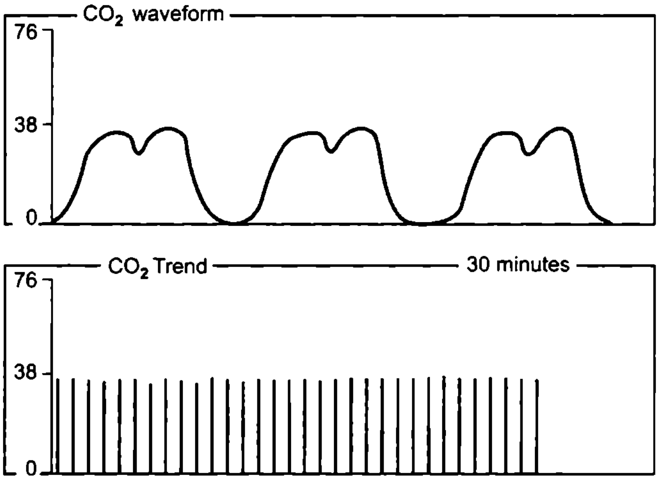

Fig. 8.9

Sudden but transient rise in $ETCO_2$ (Fig. 8.10)

- Bicarbonate therapy
- Release of a limb tourniquet

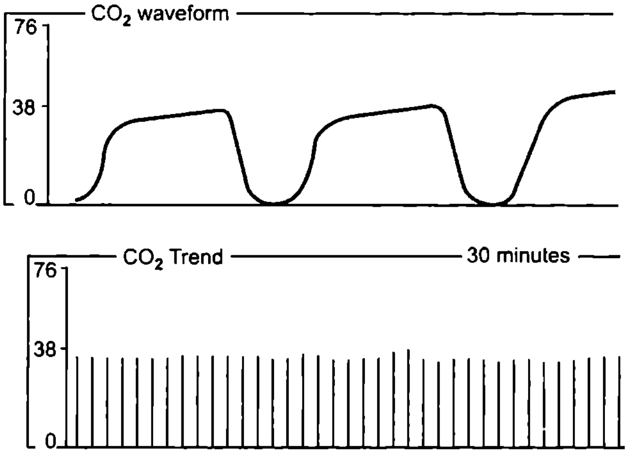

Fig. 8.10

A rising base line indicates need to re calibrate (Fig. 8.11)

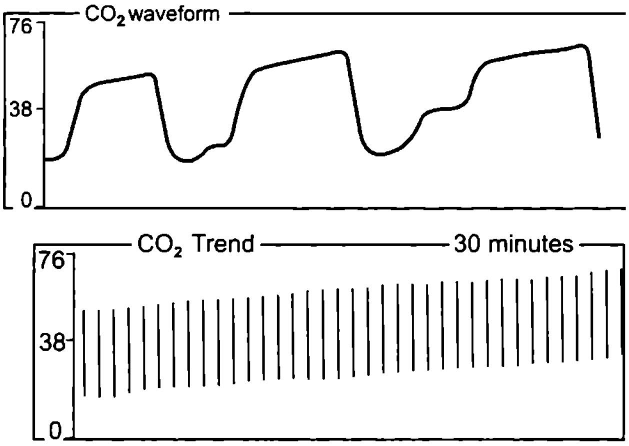

Fig. 8.11

Fig. 8.12: Capnometer ($ETCO_2$ Monitor)

Main uses in the PICU include:

- To minimize use of arterial blood gases by following trends of $ETCO_2$ (Fig. 8.12) to correct hyperventilation and hypoventilation.
- Detect secretions, partial airway obstruction, kink in endotracheal tube.
- Detect accidental disconnection of ventilatory circuit.
- Correct placement of endotracheal tube
- Esophageal tube placement
- Detect sudden hypovolemia
- In Indian settings, Routine use for end-tidal CO_2 monitor should be recommended in patients in the PICU on ventilator requiring very frequent blood gases for $PaCO_2$ determinations in order to minimize blood draw and to follow trends of $PaCO_2$.

CHAPTER

9

Pediatric Intensive Care Working Rounds and Documentation

Praveen Khilnani, Mritunjay Pao

GENERAL ADMITTING ORDERS

Following is a guideline to be used by residents and fellows for admission and daily PICU rounds with consultant/faculty.

Admitting orders on an unstable patient (shock, mechanical ventilation, encephalitis, etc.) admitted to the pediatric intensive care unit include:

1. Admit to Dr .... in PICU Level III
2. Diagnosis
3. Condition critical/labile/stable
4. Vital signs per PICU routine on cardiorespiratory monitor heart rate, respirations, blood pressure (NBP at regular cycles or intraarterial continuous)
5. Pulse oximetry continuous
6. Hourly temperature, urine output
7. Nasogastric tube
8. Foley catheter
9. Investigations: CBC, platelets, PT PTT, Na, K, Ca^{++}, urea, cr, blood culture, LFTs, ABG now
10. Chest X-ray now and every AM
11. Initial ventilator settings: tidal volume, peak pressure, PEEP, inspiratory time, rate, FiO_2
12. Inform the intensivist if:

    BP > or <
    CVP > or <
    pH > or <
    PO_2 > or <
    PCO_2 > or <
13. Paracetamol 15 mg/kg po/pr for temp >101 sos Q 4 hourly
14. Arterial line flush 2 ml/hr NS 1:1 heparinized saline
15. Fluids bolus with NS/LR 20 ml/kg as ordered
16. Maintenance fluids D5 (1/4) NS with 20 meqkcl/L after voids
17. Sedation midazolam drip at ....
18. Muscle relaxants.Vecuronium/pancuronium at ....
19. Other medications such as Ranitidine/Antibiotics/aerosols/vasoactive drips, epinephrine, dopamine, dobutamine, norepinephrine
20. Blood/fresh frozen plasma/platelets
21. Feeds/nil by mouth
22. Consults with other subspecialists

Information to be presented on daily PICU rounds by registrar or fellow: **Systematic approach by problems:**

- *Over all condition* critical/improved
- Vital signs
- *Respiratory* O_2 saturation, lung examination, FiO_2 and ventilatory settings, ABG, Chest X-ray, endotracheal tube position
- Assessment and plan
- *Cardiovascular* CVP, ABP, capillary refill, pressor drip doses. *Assessment and plan*
- *Fluids* Total intake/Output total fluid rate IV + oral
- *Hematological* HB, WBC, Platelets, PT, PTT need for blood, blood products
- *Gastrointestinal/nutrition* feeds Cal/kg/day enteral or parenteral, abdominal girth bowel sounds, aspirates/residuals
- Stool/vomiting
- *Electrolytes* Na/K/Cl/HCO_3 Ca^+/Mg *Assessment and plan*

- *Renal* urine output ml/kg/hr Urea/Cr
- Hepatic Liver functions, albumin, bilirubin, liver enzymes, amylase
- *Infectious disease* fever spikes, white counts, culture results blood, CSF, urine, tracheal aspirate. Antibiotics Days of therapy.
- *Neurological* Alertness/pupils size and reaction/ response/GCS
- EEG/last seizure/CT/MRI. Shunt related/ ventriculostomy issues.
- Neurosurgical issues.
- Physiotherapy issues
- *Social* Family visited, involved. Condition and medical care plan explained.
- Overall plan of the day.

Following section is intended to describe the various parts of documentation necessary in a world class PICU. An improved documentation strategy can only help avoid later misrepresentation,or distortion of the facts, in case of a legal suit.

All of the following are necessary to be established for any tertiary level PICU.

1. Picu protocols (including safety, pain control, infection control)
2. Admission, Discharge and transfer criteria
3. Medical incharge responsibilities
4. Staff responsibilities
5. Common medical management protocols for residents and nurses
6. Picu statistics and outcomes data keeping
7. Continuous Quality improvement/audits
8. Record keeping

This article is intended to familiarize the reader with standards of ***record keeping*** in the pediatric intensive care unit at IP Apollo hospital certified by JCI .

Record Keeping

Proper record must be maintained including history, examination and investigation reports. Treatment adopted, consent for various procedures (including refusals) and any expert opinion (if advised) should be recorded in writing. A well maintained record can be a friend of the doctor in an hour of crisis. Writing good notes is an art and complete, accurate documentation is essential. It ensures continuity of care. Don't try to manipulate the records(1).

If you don't document, you didn't see the patient So, only defense is a well written case sheet.

Following documentation should be clear and concise

Admission notes
Progress notes
Prescriptions
Procedure notes
Transfer notes
Discharge Summaries

General Guidelines

Note Heading
Date *and* Time
Legible
No erasures/White Out
Strike through mistakes and write "error"
Sign and print name, with designation
Multi page notes – sign; rewrite date and time

Admission Notes

Clear and complete admission note essential
Need not be long
Preprinted format acceptable
Document Presenting complaint, History, wit review of systems, Allergies (even if absent), pa history, Family history
Physical Examination
Investigations
Assessment
Plan

Progress Notes

Date and time
Title
S.O.A.P. format

Subjective – what the patient says/expresses. M not be practical in ventilated or comatose pediat patient. Pain score can still be performed. Moth can describe some of the problems.

Objective – what you find on examination, includi vital signs and lab results

Assessment

Plan

Signature, printed name and designation

Plan can be problem oriented for complicated patients

SOAP note - Subjective

Why is the patient here? Describe problems concisely.
Include only information pertinent to his complaints
State what the patient says
If a new patient, document past medical history, medications, allergies, family history and important social history

SOAP note - Objective

What do you see? This is the physical exam, which should be focused on the systems related to the patient's complaints
Vital signs are mandatory
Include max temperature in past 24 hours
Write the exam in order, from head to toe, even if you don't perform the examination that way
What labs or tests have been performed – list these and the results after the Physical Exam
Don't list investigations that will be done later – they go under the Plan

SOAP note - Assessment

What do you think is going on
List the diagnosis, if you are sure or possible diagnoses, if you are not
Imagine you won't be there tomorrow and someone else has to figure out why you chose the tests or treatment that you did.

SOAP note - Plan

What are you going to do?
What tests are planned and when?
What medicines are being started?

POMR (Problem oriented medical record) format

An alternate equally acceptable note can be POMR problem oriented medical record format.

Problem by System

In each system heading relevent problem, condition, investigations need to be documented, any clinical change since the last note should be documented, as well as consultant recommendations. Affected system can be detailed.other unaffected systems can be brief, but all systems heads should be mentioned to be complete.

Example

Note heading
Date time
General condition
(alert/playful/remains comatose/critical/remains ventilated/somewhat improving/stable any rashes/peticheae)
Vital signs Temperature, heart rate, blood pressure, respiratory rate pulse oximeter saturation, Capillary perfusion

Problem by system:
Respiratory (Resp)
(distress, spontaneous respiratory effort, FIO_2, ventilator settings, oxygen saturations, Lung findings on examination, blood gases, end tidal CO_2, chest X-ray, Respiratory medications/nebulization/respiratory therapy, any clinical change, any consultation)

Assessment and plan
Cardiovascular(CV)
(S1S2 normal no murmur/gallop. Blood pressure, CVP, Inotropic support dopamine at...., Adrenaline at....., other cardiovascular medications, Echocardiogram, ECG finding, any clinical change, any consultation)

Assessment and plan
Gastrointestinal (GI)
(hepatosplenomegaly, jaundice, ascitis, diarrhea/constipation
Stool number, frequency, consistency
GI bleeding, vomiting, nasogastric drainage,
Abdominal distension, tenderness, bowel sounds, liver function tests, GI medications, any clinical change, any consultation)

Assessment and plan
Fluid/nutrition(F/N)
(IV fluids type, rate, TPN, nil by mouth or feedings at ml/hr or second/third hourly, Calorie count

(kcal/kg/day), 24 hour intake out put, Net fluid balance: positive/negative, how much
Need for diuretics/fluid restriction, related lab values, albumin, triglycerides, any change, any dietary consults)

Assessment and plan
Hematological (Heme)
(hemoglobin/hematocrit/platelet count, DIC, d dimer, fibrin split products, PT, PTT, INR. any blood, fresh frozen plasm or platelet transfusions given, any clinical bleeding, severe anemia, any change, any consultations)

Assessment and plan
Infectious disease (ID)
(fevers, WBC count differential
CRP/X-ray, Ultrasound, CT/MRI findings as applicable
Blood cultures, last cultures, antimicrobials and monitoring drug levels, change in status, any consultations)

Assessment and plan
Renal(Renal)
(Urine out put, Urea, creatinine, blood pressure, serum potassium, acid base status. Overall fluid balance, medications, any change, consultations, Dialysis modality, Peritoneal Dialysis, hemodialysis, hemofiltration, kidney biopsy if applicable, lab results)

Assessment and plan
Metabolic
(Acid base status, anion gap if any, lactic acidosis, diabetic ketoacidosis, sodium, potassium, calcium, magnesium, phosphorus, glucose abnormalities, insulin therapy, any change, any consultations)

Assessment and Plan
Neurological
(GCS and Mental status, pupils reactive, non reactive, equal unequal, cranial nerves, motor sensory deficits, last seizure, ICP/ventriculostomy drain as applicable, CT, MRI, EEG findings. Medications including seizure medications.
Medication levels (serum), mannitol, steroids, EMG, VEP, BERA, Sedation and muscle relaxation, any significant clinical change, any new consultations)

Assessment and plan
Social
family here, involved, parents counselled. Problems discussed with family.
Overall assessment
1.
2.
3.
4.

Overall Plan (after discussion with involved multidisciplinary consultants in complex patients)
1.
2.
3.
4.

IMPORTANT POINTS TO REMEMBER

Always be truthful
If you didn't examine a system, leave it blank - don't make things up
Never add to (or delete from) an old note or chart. Make a new, corrected entry – the walls have copying machines!
Document what you tell the family

Abbreviations

Do not use non standard abbreviations (or even standard abbreviations limited to a specialty) – e.g. *TOF.*

Prescription Do's and Don'ts

For as needed drugs, do write "PRN" or "SOS", with the parameters for giving a dose
To discontinue(DC) an order, do write a DC order – do not just cross it out
To correct an order, strike through and rewrite
Do not add to an order after the nurse has seen and signed off
For drugs where serum levels correlate with therapeutic response, write dosing intervals (q 8 hrs or q 12 hrs), rather than bd or tds (antibiotics, CVS drugs, Theophylline, antiarrhythmics etc).

Verbal or phone orders have to be signed within 24 hours
Do not order in amps, mL or tablets
Eptoin suspension 30 mg/5 mL
Dilantin suspension 25 mg/mL = 125 mg/5 ml
Eptoin tablets 50 mg and 100 mg
Always discuss the order with the nurse to make sure there is no misunderstanding
Do write and sign legibly
Procedure Notes
Name of the procedure
Indication
Whether informed consent obtained (Obtain a written consent)
Site
What sedation and analgesia were used
Actual procedure, including equipment used
Condition after the procedure
Complications
Any confirmatory tests performed
Include: Intubation, arterial and Central lines, Chest tubes, LP, Bone Marrow aspiration
Write a note even if procedure is unsuccessful

Transfer Note

Transfer from ICU to Ward or to another hospital
Especially important if long length of stay
Brief summary, including:
Presentation, treatment, hospital course, relevant investigations, procedures, complications, current medications and labs to be followed up
Transfer orders
Write clear and unambiguous transfer orders
(All previous orders to be discontinued, to avoid confusion)

When transfer to another hospital accepting physician, patient condition and mode of transfer must be documented

Discharge Summary

Others will judge us by the quality of the Discharge Summary
Put yourself on the receiving end.
Brief clinical summary, including
Presentation, relevant investigations, diagnosis, treatment, hospital course, procedures, complications, outcome
Discharge medications and advice
Follow up

SUMMARY

General recommendations for documentation
Use complete sentences
Avoid unnecessary detail
Pay attention to spelling and grammar
Avoid wordiness and jargon
"clouded sensorium with decreased mental status" = confused
"integumentary apparatus" = skin
"ambulate" = walk
"...experienced a rapidly fatal outcome" = died

APPENDIX

Informed consent : Pediatric intensive care unit

Name age sex M F
Reg no

I .... father/mother of above named patient hereby authorize Dr. .... and those whom he may designate as associates or assistants to perform following emergency procedures in the pediatric intensive care unit.

Resuscitation
Endotracheal intubation
Initiation of mechanical ventilation
Central line placement
Arterial line placement

*I further consent to administration of intravenous sedation to assist in above mentioned procedures

*I further consent to administration of such drugs, infusions, plasma or blood products transfusion or any other treatment or procedure deemed necessary in the judgement of medical staff.

*I consent to have my/my wards blood tested for infectious diseases such as hepatitisB,Cand,HIV

*The nature and purpose of the procedures ,the necessity thereof, the possible alternative methods of treatment, the risks involved and the possibility of complication in the treatment of my/my wards condition have been fully explained to me and I understand the same.

I certify that I have read and fully understood the above consent, that the explanations therein referred to were made and that all blank statements requiring insertion or completion were filled in and any inapplicable paragraphs stricken before I signed.

Signature of doctor/ witness	Name..
.... Date time	Relationship to patient......... Signature of patient/person authorized to consent for the patient..........

CHAPTER

10

Nursing Care in the PICU

Praveen Khilnani, Sister Gracey

Nursing in pediatric intensive care is a challenging job since prime responsibility of a nurse is to not only help save the critically ill child but in addition deal with the family members who are highly stressed. The following chapter is intended for a pediatric ICU nurse to orient oneself with the PICU environment and work as a team on various issues related to medical management of a critically ill child and to provide emotional and psychological support to the family.

For the efficient functioning of the unit the nurse incharge should keep the equipment and supplies needed for the unit ready at all times.

All equipment should be checked daily for its proper functioning including the defibrillator and the entire resuscitation cart. Written protocols should be available in the unit regarding the use of all equipment and various procedure.

Routinely used equipment for PICU admission:

- Cardiac monitor system with ECG, pulse oximeter, NIBP, invasive pressure and temperature module.
- Centrally supplied oxygen and suction.
- Crash cart with emergency drugs supplies for resuscitation, laryngoscopes, endotracheal tubes and stylet pediatric size mask pediatric airway laryngeal mask airways, ambu bag, C-circuit bag.
- Intubation medications: Morphine, midazolam, ketamine, succinylcholine, atropine, Vecuronium, rocuronium, etc.
- Defibrillator
- Mechanical Ventilator
- Suction (6, 8, 10 fr) catheters

Facilities for invasive and noninvasive procedures

- Central lines, multilumen 4 french, 5.5 french and 7 french sizes
- Arterial line catheters 22 g and 24 g with 15 and 18 fr guidewires
- Chest tubes 10, 12, 16, 20 french
- Infusion tubings
- Threeway stopcock
- Syringes of 2, 5, 10, 20 and 60 cc
- Normal saline and Ringer's lactate
- Invasive pressure transducer
- Infusion pumps

When transporting the patient a doctor and a nurse should accompany the child. He/she should be able to resuscitate the patient on the way if any emergency arises. The patient should be transported with a cardiac monitor and a pulse oximeter, with resuscitation supplies such as laryngoscope, endotracheal tube, oxygen and ambu bag. While transferring the patient from bed to transport cart/ CT/MRI table, the leads, wires, tubes, catheters should be handled carefully with prime attention to the secure airway/endotracheal tube.

Repeated nursing assessment of the critically patient should provide for the following at the minimum:

- To establish a patent airway
- To ensure that patient is breathing adequately
- To check for adequate circulation.

For a critically ill patient who requires endotracheal (ET) intubation and ventilatory support.

Nurse should have the following supplies:

1. 'C' circuit and ambu bag with proper size mask
2. Laryngocope with different size blades.

3. Flexible stylet to be used as a guide during endotracheal tube insertion.
4. Lubricant jelly to lubricate tube.
5. Syringes for inflating ET tube and for medications.
6. Oral airway to prevent patient biting on the tube.
7. Sterile gloves
8. O_2 supply and suction and suction catheter
9. Sedation and muscle relaxant
10. Adhesive plaster to fix the ET tube.
11. Endotracheal tubes (ET tubes).

Approximate OD (outer diameter) size of the ET tubes for different age group:

Size of the ETT = Age in years/4 +4

• New born to 1 year	2.5 mm – 4 mm
• 1 year to 4 years	4 mm – 4.5 mm
• Older children upto 10 years	5 mm – 7 mm

Vital signs and pulse oximeter saturations should be checked and recorded before, during and after intubation.

After the ET tube insertion connect the C circuit or ambu bag and ventilate the lung. Auscultate the chest for equal air entry, watch for chest movement. Endtidal CO_2 indicator can also be used to confirm proper placement of endotracheal tube. In case of esophageal intubation endtidal CO_2 will be zero. If the oxygen saturations and chest movements are adequate, fix the ET tube disconnect the patient from the C circuit and connect the patient to the ventilator with preset parameters set by the doctor. X-ray chest is required to check the tube position.

Basic Life Support Protocol (Fig. 10.1)

All PICU nurses need to be BLS and PALS trained, and be familiar with resuscitation protocol. Nurse needs to be familiar with resuscitation code cart, its equipment, defibrillator, bag mask ventilation. Following is a protocol from American heart association applicable on all unresponsive patient. (AED, automatic external defibrillator) is not universally available and dialing 911 doesn't apply in Indian situation).

BRADYCARDIA ALGORITHM (FIG. 10.2)

The emergency treatment of bradycardia depends on its hemodynamic consequences. In patients with bradycardia that is causing cardiorespiratory compromise:

1. Support airway, breathing, and circulation as needed, administer oxygen, and attach a monitor/defibrillator.
2. If pulses, perfusion, and respiration are normal, no emergency treatment is necessary. Monitor and proceed with evaluation.
3. If heart rate remains <60 beats per minute with poor perfusion despite effective ventilation with oxygen, start chest compressions.
4. Reevaluate the patient to determine if signs of hemodynamic compromise persist despite the support of adequate oxygenation and ventilation and compressions if indicated. Verify that the support is adequate—e.g. check airway and oxygen source and effectiveness of ventilation.
5. Continue to support airway, ventilation, oxygenation (and provide compressions as needed) and give epinephrine. If bradycardia persists or responds only transiently, consider a continuous infusion of epinephrine or isoproterenol. If bradycardia is due to vagal stimulation, give atropine.
6. Emergency transcutaneous pacing may be life saving if the bradycardia is due to complete heart block or sinus node dysfunction unresponsive to ventilation, oxygenation, chest compressions, and medications, especially if it is associated with congenital or acquired heart disease. Pacing is not useful for asystole or bradycardia due to postarrest hypoxic/ischemic myocardial insult or respiratory failure.

TACHYCARDIA ALGORITHM (FIG. 10.3)

If pulses are palpable and the patient has signs of hemodynamic compromise (poor perfusion, tachypnea, and weak pulses), ensure that the airway is patent, assist ventilations if necessary, administer supplementary oxygen, and attach an ECG monitor or defibrillator. Assess QRS duration: determine if the QRS duration is 0.08 second (narrow-complex tachycardia) or >0.08 second (wide-complex tachycardia).

Narrow-Complex (0.08 Second) Tachycardia

Evaluation of a 12-lead ECG and the patient's clinica presentation and history differentiates probable

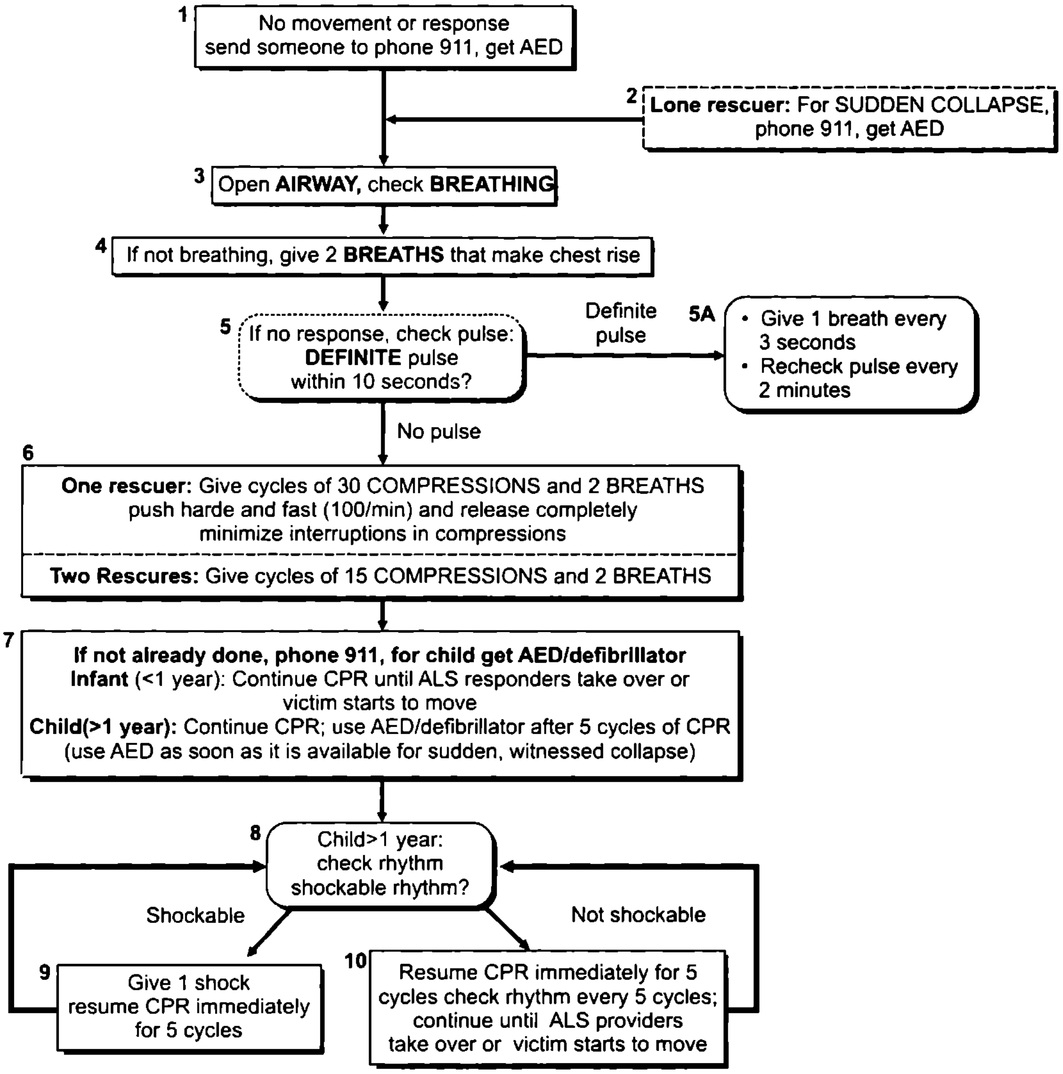
1
No movement or response
send someone to phone 911, get AED
2
Lone rescuer: For SUDDEN COLLAPSE,
phone 911, get AED
3
Open AIRWAY, check BREATHING
4
If not breathing, give 2 BREATHS that make chest rise
5
If no response, check pulse:
DEFINITE pulse
within 10 seconds?
Definite
pulse
5A
• Give 1 breath every
3 seconds
• Recheck pulse every
2 minutes
No pulse
6
One rescuer: Give cycles of 30 COMPRESSIONS and 2 BREATHS
push harde and fast (100/min) and release completely
minimize interruptions in compressions
Two Rescures: Give cycles of 15 COMPRESSIONS and 2 BREATHS
7
If not already done, phone 911, for child get AED/defibrillator
Infant (<1 year): Continue CPR until ALS responders take over or
victim starts to move
Child(>1 year): Continue CPR; use AED/defibrillator after 5 cycles of CPR
(use AED as soon as it is available for sudden, witnessed collapse)
8
Child>1 year:
check rhythm
shockable rhythm?
Shockable
Not shockable
9
Give 1 shock
resume CPR immediately
for 5 cycles
10
Resume CPR immediately for 5
cycles check rhythm every 5 cycles;
continue until ALS providers
take over or victim starts to move

Fig. 10.1: BLS flow chart

sinus tachycardia from probable supraventricular tachycardia (SVT). If the rhythm is sinus tachycardia, search for and treat reversible causes.

Probable Supraventricular Tachycardia

Monitor rhythm during therapy to evaluate effect. The choice of therapy depends on the patient's degree of hemodynamic instability.

1. Attempt *vagal stimulation* first unless the patient is very unstable and if it does not unduly delay chemical or electrical cardioversion. In infants and young children, apply ice to the face without occluding the airway. In older children, carotid sinus massage or Valsalva maneuvers are safe (have the child blow through an obstructed straw). Avoid pressure to the eye because this can damage the retina.
2. If there is no response to vagal maneuvers or if the patient is unstable use chemical cardioversion with adenosine (very effective). Administer adenosine using 2 syringes connected to a T-connector or stopcock; give adenosine rapidly with one syringe and immediately flush with 5 mL of normal saline with the other.
3. If IV access is not readily available, provide electrical (synchronized) cardioversion. Consider sedation if possible. Start with a dose of 0.5 to 1 J/kg. If unsuccessful, repeat using a dose of 2 J/kg. If a second shock is unsuccessful or the

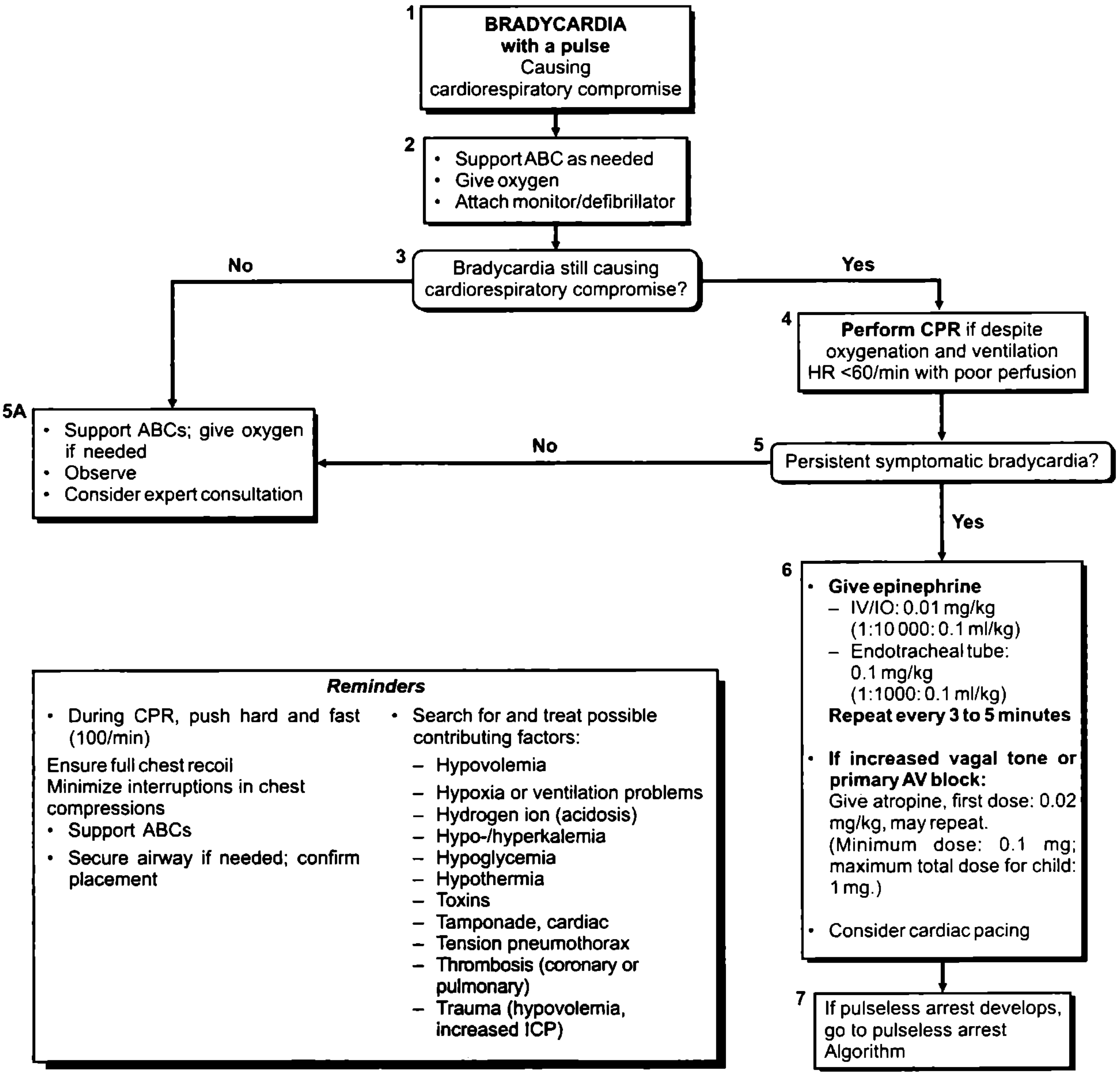
1
BRADYCARDIA
with a pulse
Causing
cardiorespiratory compromise
2
• Support ABC as needed
• Give oxygen
• Attach monitor/defibrillator
3
Bradycardia still causing
cardiorespiratory compromise?
No
Yes
4
Perform CPR if despite
oxygenation and ventilation
HR <60/min with poor perfusion
5A
• Support ABCs; give oxygen if needed
• Observe
• Consider expert consultation
No
5
Persistent symptomatic bradycardia?
Yes
6
• Give epinephrine
– IV/IO: 0.01 mg/kg
(1:10 000: 0.1 ml/kg)
– Endotracheal tube:
0.1 mg/kg
(1:1000: 0.1 ml/kg)
Repeat every 3 to 5 minutes
• If increased vagal tone or primary AV block:
Give atropine, first dose: 0.02 mg/kg, may repeat.
(Minimum dose: 0.1 mg; maximum total dose for child: 1 mg.)
• Consider cardiac pacing
7
If pulseless arrest develops, go to pulseless arrest Algorithm
Reminders
• During CPR, push hard and fast (100/min)
Ensure full chest recoil
Minimize interruptions in chest compressions
• Support ABCs
• Secure airway if needed; confirm placement
• Search for and treat possible contributing factors:
– Hypovolemia
– Hypoxia or ventilation problems
– Hydrogen ion (acidosis)
– Hypo-/hyperkalemia
– Hypoglycemia
– Hypothermia
– Toxins
– Tamponade, cardiac
– Tension pneumothorax
– Thrombosis (coronary or pulmonary)
– Trauma (hypovolemia, increased ICP)

Fig. 10.2: Bradycardia algorithm

tachycardia recurs quickly, consider antiarrhythmic therapy (amiodarone or procainamide) before a third shock.

4. Consider amiodarone or procainamide for SVT unresponsive to vagal maneuvers and adenosine Use extreme caution when administering more than one drug that causes QT prolongation (e.g., amiodarone and procainamide). Consider obtaining expert consultation. Give an infusion of amiodarone or procainamide slowly (over several minutes to an hour), depending on the urgency, while you monitor the ECG and blood pressure. If there is no effect and there are no signs of toxicity, give additional doses. Do no use verapamil in infants because it may cause refractory hypotension and cardiac arrest, and use with caution in children because it may cause hypotension and myocardial depression.

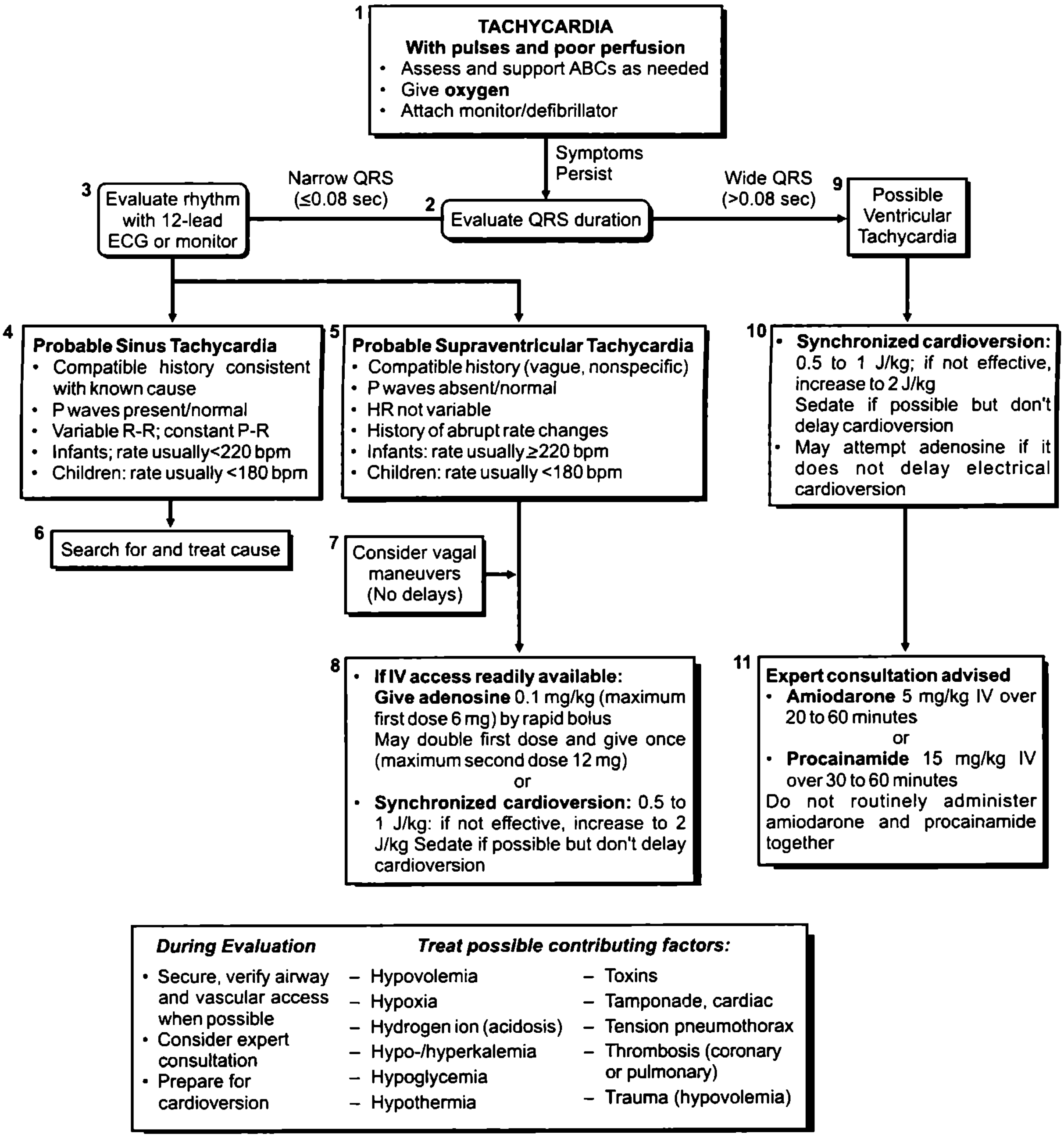
1
TACHYCARDIA
With pulses and poor perfusion
• Assess and support ABCs as needed
• Give oxygen
• Attach monitor/defibrillator
Symptoms Persist
2
Evaluate QRS duration
Narrow QRS (≤0.08 sec)
3
Evaluate rhythm with 12-lead ECG or monitor
Wide QRS (>0.08 sec)
9
Possible Ventricular Tachycardia
4
Probable Sinus Tachycardia
• Compatible history consistent with known cause
• P waves present/normal
• Variable R-R; constant P-R
• Infants; rate usually<220 bpm
• Children: rate usually <180 bpm
5
Probable Supraventricular Tachycardia
• Compatible history (vague, nonspecific)
• P waves absent/normal
• HR not variable
• History of abrupt rate changes
• Infants: rate usually≥220 bpm
• Children: rate usually <180 bpm
10
• Synchronized cardioversion: 0.5 to 1 J/kg; if not effective, increase to 2 J/kg
Sedate if possible but don't delay cardioversion
• May attempt adenosine if it does not delay electrical cardioversion
6
Search for and treat cause
7
Consider vagal maneuvers (No delays)
8
• If IV access readily available:
Give adenosine 0.1 mg/kg (maximum first dose 6 mg) by rapid bolus
May double first dose and give once (maximum second dose 12 mg)
or
• Synchronized cardioversion: 0.5 to 1 J/kg: if not effective, increase to 2 J/kg Sedate if possible but don't delay cardioversion
11
Expert consultation advised
• Amiodarone 5 mg/kg IV over 20 to 60 minutes
or
• Procainamide 15 mg/kg IV over 30 to 60 minutes
Do not routinely administer amiodarone and procainamide together
During Evaluation
• Secure, verify airway and vascular access when possible
• Consider expert consultation
• Prepare for cardioversion
Treat possible contributing factors:
– Hypovolemia
– Hypoxia
– Hydrogen ion (acidosis)
– Hypo-/hyperkalemia
– Hypoglycemia
– Hypothermia
– Toxins
– Tamponade, cardiac
– Tension pneumothorax
– Thrombosis (coronary or pulmonary)
– Trauma (hypovolemia)

Fig. 10.3: Tachycardia algorithm

Wide-Complex (> 0.08 Second) Tachycardia

Wide-complex tachycardia with poor perfusion is probably ventricular in origin but may be supraventricular with aberrancy. Treat with synchronized electrical cardioversion (0.5 J to 1 J/kg). If it does not delay cardioversion, try a dose of adenosine first to determine if the rhythm is SVT with aberrant conduction. If a second shock (2 J/kg) is unsuccessful or if the tachycardia recurs quickly, consider antiarrhythmic therapy (amiodarone or procainamide) before a third shock.

Tachycardia with Hemodynamic Stability

For VT, give an infusion of amiodarone slowly (minutes to an hour depending on the urgency) while you monitor the ECG and blood pressure. If there is no effect and there are no signs of toxicity, give additional doses. If amiodarone is not available, consider giving procainamide slowly (over 30 to 60 minutes) while you monitor the ECG and blood pressure. Do not administer amiodarone and procainamide together without expert consultation. Because all arrhythmia therapies have the potential for serious adverse effects, consider consulting an expert in pediatric arrhythmias before treating children who are hemodynamically stable.

PULSELESS ARREST

If a victim becomes unresponsive, start BLS protocol. Start CPR immediately (with supplementary oxygen if available) and send for a defibrillator (manual or automated external defibrillator [AED]). Asystole and bradycardia with a wide QRS complex are most common in asphyxial cardiac arrest. VF and pulseless electrical activity (PEA) are less common and more likely to be observed in children with sudden arrest. If you are using an ECG monitor, determine the rhythm; if you are using an AED, the device will tell you whether the rhythm is "shockable" (i.e. VF or rapid VT), but it may not display the rhythm.

"Shockable Rhythm": VF/Pulseless VT

VF occurs in 5 to 15% of all pediatric victims of out-of-hospital cardiac arrest and is reported in up to 20% of pediatric in-hospital arrests at some point during the resuscitation. The incidence increases with age. Defibrillation is the definitive treatment for VF (Class I) with an overall survival rate of 17% to 20%, but in adults the probability of survival declines by 7% to 10% for each minute of arrest without CPR and defibrillation. The decline in survival is more gradual when early CPR is provided.

Defibrillators

Defibrillators are either manual or automated (AED), with monophasic or biphasic waveforms. Institutions that care for children at risk for arrhythmias and cardiac arrest (e.g. hospitals, emergency departments) ideally should have defibrillators available that are capable of energy adjustment that is appropriate for children. Many AED parameters are set automatically. Use the largest paddles or self-adhering electrodes that will fit on the chest wall without touching (leave about 3 cm between the paddles). Adult paddles (8 to 10 cm) for children >10 kg (more than approximately 1 year of age). Infant paddles for infants weighing <10 kg. The electrode–chest wall interface can be gel pads, electrode cream, paste, or self-adhesive monitoring-defibrillation pads. Apply firm pressure on the paddles (manual) placed over the right side of the upper chest and the apex of the heart (to the left of the nipple over the left lower ribs). Alternatively place one electrode on the front of the chest just to the left of the sternum and the other over the upper back below the scapula.

Energy Dose

The lowest energy dose for effective defibrillation and the upper limit for safe defibrillation in infants and children are not known. Biphasic shocks appear to be at least as effective as monophasic shocks and less harmful. With a manual defibrillator (monophasic or biphasic), use a dose of 2 J/kg for the first attempt and 4 J/kg for subsequent attempts.

AEDs (automatic external defibrillators)

Many AEDs can accurately detect VF in children of all ages and differentiate shockable from non-shockable rhythms with a high degree of sensitivity and specificity. AEDs can be safely and effectively used in children 1 to 8 years of age. There is insufficient data to make a recommendation for or against using an AED in infants <1 year of age. When using an AED for children about 1 to 8 years old, use a pediatric attenuator system, which decreases the delivered energy to a dose suitable for children. If an AED with a pediatric attenuating system is not available, use a standard AED, preferably one with sensitivity and specificity for pediatric shockable rhythms.

Defibrillation Sequence

If VF or Pulseless VT is present follow the following steps:

1. Attempt defibrillation immediately. The earlier you attempt defibrillation, the more likely the attempt will be successful.
2. Provide CPR until the defibrillator is ready to deliver a shock.

3. Give first shock (2 J/kg) as quickly as possible and immediately resume CPR, beginning with chest compressions. If 1 shock fails to eliminate VF, the incremental benefit of another shock is low, and resumption of CPR is likely to confer a greater value than another shock. CPR may provide some coronary perfusion with oxygen and substrate delivery, increasing the likelihood of defibrillation with a subsequent shock. Check the rhythm. Continue CPR for about 5 cycles (about 2 minutes).
4. Check the rhythm. If a shockable rhythm persists, give second shock (4 J/kg), resume compressions immediately. Give a dose of epinephrine. Use a standard dose of epinephrine (.01mg/kg) for the first and subsequent doses. There is no survival benefit from routine use of high-dose epinephrine, and it may be harmful, particularly in asphyxia. Give the standard dose of epinephrine about every 3 to 5 minutes during cardiac arrest.
5. After 5 cycles (approximately 2 minutes) of CPR, check the rhythm. If the rhythm continues to be "shockable," deliver a shock (4 J/kg), resume CPR (beginning with chest compressions) immediately, and give amiodarone or lidocaine if you do not have amiodarone while CPR is provided. Continue CPR for 5 cycles (about 2 minutes) before again checking the rhythm and attempting to defibrillate if needed with 4 J/kg.
6. Once an advanced airway is in place, the compressing rescuer should give continuous chest compressions at a rate of 100 per minute without pauses for ventilation. The rescuer delivering ventilation provides 8 to 10 breaths per minute. Two or more rescuers should rotate the compressor role approximately every 2 minutes to prevent compressor fatigue and deterioration in quality and rate of chest compressions.
7. If you have a monitor or an AED with a rhythm display and there is an organized rhythm at any time, check for a pulse and proceed accordingly.
8. If defibrillation is successful but VF recurs, continue CPR while you give another bolus of amiodarone before you try to defibrillate with the previously successful shock dose (see Box 8). Search for and treat reversible causes.

CARE OF THE HEMODYNAMICALLY UNSTABLE VENTILATED PEDIATRIC PATIENT

Cardiorespiratory Monitors

Cardiorespiratory monitors are part of the basic standard in the PICU.

Principle A sensor system consisting of electrodes is applied to the patient to detect electrical activity from the heart. This signal is amplified and displayed as waveform, i.e. electrocardiogram (ECG). A display of the rate and pattern of the chest wall movements is called pneumography. There is a wide variety of these monitors. The most important features are display of the ECG, tracing, and respiratory movement with at least two channels for invasive pressure monitoring. Most monitors come with a built in pulse oximeter and a non-invasive automated blood pressure monitor (Hewlett Packard, BPL, Ohmeda).

These monitors should allow for adjustment of the signal intensity, have a numeric read out, save information in memory, and transmit it to another monitor and/or central station if possible. Monitors must be equipped with audio and visual alarms for parameters that can be set to the particular needs of a patient, e.g. apnea at 10, 15, or 20 seconds. The possibility of printing the information stored on the monitor is a very attractive feature, but may not be affordable in all units. High and low rate alarms can be set on these monitors.

Troubleshooting Proper placement of electrodes is crucial. The skin must be clean and dry. Standard electrodes with lubricating conductive jelly may be used. The electrodes measuring impedance of the chest should be placed on each side of the chest. It should be remembered that the detection of chest wall movement does not necessarily reflect an effective volume, e.g. airway obstruction may not be detected even though chest movements are adequate. Certain types of electrodes may irritate the skin in some patients.

Hemodynamic Monitoring

This is indicated in any patient admitted to the pediatric intensive care unit (PICU) who is in shock, has respiratory failure, or has sustained an acute neurologic insult. Included in hemodynamic monitoring are heart rate and blood pressure as well as CVP and pulmonary capillary wedge pressure (PCWP) and, occasionally in postoperative cardiovascular patients, right atrial and left atrial pressures (RA and LA lines). Heart rate can be measured with conventional electrodes placed on the chest, which can also provide rhythm strips usually in lead II. The lead can be changed if indicated to evaluate for other dysrhythmias, but it should not substitute for a 12-lead electrocardiogram (ECG).

Blood pressure is determined invasively and non-invasively. The choice is determined by the instability of the patient, skill levels of the physicians, and ability of the staff to maintain such devices. Non-invasive blood pressure monitoring provides for manual or automatic repeated but intermittent readings of blood pressure. Whether one chooses a conventional sphygmomanometer or an ultrasonic/ Doppler device, appropriate cuff sizes are required to obtain an accurate blood pressure. The cuff should encompass approximately two-thirds of the length of the part of the extremity from which it is measuring. The upper arm, lower leg, and upper leg offer the best sites for obtaining non-invasive blood pressures. Besides the cuff size, factors that affect peripheral blood flow or pulmonary vascular resistance or produce significant peripheral edema may result in abnormal values for non-invasively measured blood pressure.

Automated Non-invasive Blood Pressure (NIBP) Monitoring

Principle Non-invasive blood pressure measurements are done automatically using oscillometric principle, or a Doppler technique.

Oscillometry Equipment consists of an inflatable occlusive cuff connected via a double plastic tubing to an inflating pump and to a pressure transducer, e.g. Dinamap. Oscillations in the artery are produced after an automatic inflation, and deflation of the cuff. Oscillations detected are transformed into an electrical current, integrated into a microprocessor, and digitally displayed. The cuff inflates above the systolic pressure occluding the artery. As the cuff is deflated, the artery opens, blood spurts through, and there is detection of the oscillations which determines the systolic BP. The cuff pressure continues to decrease and the point where maximal oscillations are detected represents the mean arterial BP. As the cuff pressure decreases, there is a point where the artery remains open and the oscillations are uniform with minimal amplitude; this is the diastolic BP. This technique reflects mean arterial pressure fairly, accurately, but in comparison with intra-arterial pressures, it may show a higher diastolic pressure reading. It has a tendency to get a lower reading of high systolic blood pressure and a higher reading of low systolic pressures.

Doppler Ultrasonic Technique

It functions by ultrasonic detection of the arterial wall motion when the cuff is deflated. Audible sounds similar to Korotkoff sounds are emitted. It is described as being more reliable in cases of hypotension or shock, and being unaffected by artifacts created by patient motion or acoustics.

Troubleshooting. To avoid pitfalls, it is important to keep the cuff at the level of the heart, the width of the cuff should encircle at least two-thirds of the extremity, and kinking of the tubing should be avoided. A limb that has an arterial line or where an infusion is being administered should not be used.

Care of Ventilatory Issues Related to Nursing

Patient ventilator dysynchrony:Incoordination between the patient and the ventilator:Patient fights the ventilator!!

Common causes include, Hypoventilation, hypoxemia, tube block/ kink/malposition, bronchospasm, pneumothorax, silent aspiration, increased oxygen demand/increased CO_2 production(in sepsis), inadequate sedation.

If patient fighting the ventilator and desaturating: Immediate measures.

USE : D O P E

D Displacement, O Obstruction, P Pneumothorax, E Equipment failure

1. Check tube placement. When in doubt take the endotracheal tube out, start manual ventilation with 100% oxygen
2. Examine the patient: is the chest rising? Breath sounds present and equal? Changes in exam?

Atelectasis, treat bronchospasm/tube block/ malposition/pneumothorax? (Consider needle thoracentesis)

Examine circulation: shock? Sepsis?

3. Check arterial blood gas and chest x ray for worsening lung condition, and for confirming pneumothorax.
4. Examine the ventilator, ventilator circuit/ humidifier/gas source

If no other reason for hypoxemia :increase sedation/muscle relaxation, put back on ventilator.

Sedation and muscle relaxation during ventilation

Most patients can be managed by titration of sedation without muscle relaxation.

Midazolam (0.1-0.2 mg/kg/hr) and vecuronium drip (0.1-0.2 mg/kg/hr) is most commonly used. Morphine or fentanyl drip can also be used if painful procedures are anticipated.

Routine Ventilator Management Protocol

Following protocol is commonly followed

1. Wean FIO_2 for SpO_2 above 93-94.
2. ABG one hour after intubation, then am pm schedule (12 hourly), and after major ventilator settings change, and 20 min after extubation.
3. Pulse oximetry on all patients, End tidal carbon dioxide ($ETCO_2$)/graphics monitoring if available.
4. frequent clinical examination for respiratory rate, breath sounds, retractions, color.
5. Chest X-ray every day/alternate day/as needed.

PULSE OXIMETRY

Monitoring of pulse oximetry saturations is an essential tool in every patient on oxygen therapy as well as every ventilated patient in the PICU.

Following is an example of institutional nursing policy for use of pulse oximetry

Policy: All nurses working in the ICU and general wards may record pulse oximetry to assess respiratory function and oxygen therapeutical needs.

Nurses using this equipment should have a basic understanding of pulse oximeters and the need to obtain an adequate waveform.

Pulse oximetry is a vital tool for providing continuous observation in a safe and non invasive way.

Goals to be achieved are to obtain accurate and satisfactory information from pulse oximetry to assess ineffective management of oxygen therapy needs.

Outcomes: Maintenance of adequate oxygen therapy and prevention of respiratory difficulty.

Maintenance of patient safety.

Procedure: Fingernail bed should be clean and free of nail polish.

Probe light source should be placed on finger or ear.

Monitor visual and audible displays should be observed to assess if a strong pulse is achieved.

Special considerations: Use of oximetry increases patient safety both intra and post operatively.

Falling percentiles in oximetry readings should be brought to the physician's attention as soon as possible to enable adequate oxygen therapy be maintained.

Capnography

End-tidal CO_2 ($ETCO_2$) analysis (capnography) measures the PCO_2 in the exhaled gas. This technique is used in patients who are intubated and have minimal lung disease without significant intrapulmonary shunting. Capnography is based on the principle that the highest concentration of CO_2 sampled in the respiratory circuit represents the alveolar CO_2 concentration, which should also be close to the arterial ($PaCO_2$) concentration. Gas is constantly monitored from a side port to the connector from the ventilator to the endotracheal tube. A small amount of gas is diverted from the respiratory circuit and analyzed in a spectrophotometer for Pco_2 determination. The removal of small amounts of respiratory gas must be accounted for when calculating delivered and exhaled tidal volumes.

When interpreting $EtCO_2$ results, one needs to evaluate the graphic picture of the exhalation capnographic image to ensure that the alveolar plateau and peak are achieved. Patients who have significant intrapulmonary shunts or are spontaneously breathing may not produce an acceptable capnographic trace, and thus invalidate end-tidal CO_2 monitoring. This device permits trending and the potential for weaning of patients from mechanical ventilation; it does not replace blood gas analysis.

Capnography can also determine if one has intubated the trachea and is useful in emergent intubations. Using an analyzer that changes color on exposure to levels of CO_2 enables one to differentiate between an esophageal and tracheal intubation. The CO_2 concentration in the stomach is very low, approaching atmospheric levels of close to zero, whereas that in the lungs is markedly higher. With cardiopulmonary arrest and absent pulmonary blood flow, $ETCO_2$ will also be undetectable. Indeed, successful reestablishment of the circulation can also be assessed by an elevation of $ETCO_2$.

Position Changes

Two hourly changing of position is required. Since, ventilated children undergo numerous invasive procedures, these skin sites requires special assessment and intervention to promote healing and prevent infection. Bed linens and any clothing are kept dry and free of wrinkles. While doing X-rays or shifting the patient for any procedures nurse must check endotracheal tube, all the invasive lines, dressings, chest movements.

Mouth Care

Should be given frequently since the mouth tends to become dry. Glycerin or vaseline can be applied on lips to protect them from drying, cracking or blistering. The eyes should be checked regularly and carefully for early signs of irritation or inflammation.

Eye Care

A ventilated patient is often heavily sedated and may be even paralyzed. This predisposes the individual to exposure keratitis, corneal ulceration and infection. Along with passive closure of the eyelid, using lubricants at scheduled intervals has been shown to provide protection from above mentioned problems. The exact lubricant and the number of times to use it have not been established. At authors institution artificial tears (moisol) are placed in the eyes every 1 to 2 hours, in all cases eyes are closed shut with guaze dressing or micropore tape to protect the eyes from possible damage to cornea or the conjunctiva.

Respiratory Care During Ventilation

General

1. Position change 2 hourly right chest tilt/left chest tilt/supine position.
2. Suction 4 hourly and as needed(In line suction to avoid de recruitment/loss of PEEP/desaturation if available).
3. Physiotherapy 8 hourly
   Percussion, vibration and postural drainage.NO physiotherapy if labile oxygenation such as ARDS (Acute respiratory distress syndrome), PPHN (persistent pulmonary hypertension of neonate).
3. Nebulization : In line nebulization is preferred over manual bagging. Metered dose inhalers (MDIs) can also be used.
4. Disposable Circuit change every 72 hours.
5. Humidification/In line disposable humidifier.

Chest Physiotherapy (CPT)

Despite the extensive use of chest physiotherapy in pediatric practice there is very scant information available on its use in Mechanically Ventilated children. There is very little evidence for the beneficial effect of chest physiotherapy (CPT). Its use is well established only in acute atelectasis and pediatric lung abscess in children greater than 7 years. Prolonged immobilization and supine positioning leads to atlectasis especially of the left lower lobe, due to the weight of the heart. This in turn leads to retention of secretions superadded bacterial infection and nosocomial pneumonia.

The physiological rationale behind CPT is to mobilize secretions, prevent pneumonia and reduce hospital stay. CPT consists of a series of maneuvers such as positioning, percussion, vibration and manual hyperinflation.

Positioning: In order to increase drainage of secretion, improve ventilation/perfusion (V/Q) matching, improve oxygenation, decrease work of breathing and increase functional residual capacity (FRC) certain body positions are utilized in the ICU. These include the upright posture in a person who has obesity, ascites, abdominal surgery, or the 45° angle to decrease the risk of aspiration in a person being enterally fed.

A person with unilateral lung disease is to be placed with the affected lung uppermost in order to improve drainage of secretion and also for a better V/Q matching (as both perfusion and ventilation will increase in the gravitationally assisted normal lung). One should however remember the risk of suppurative secretions draining into the normal lung and worsening the disease process. Prone positioning has been shown to improve oxygenation in upto 85% of patients in the early stages of ARDS by increasing FRC, increasing V/Q matching, enabling drainage of secretions and improving lymphatic drainage.

Percussion and Vibration: Percussion is performed by manually clapping the chest wall using cupped hands. It is done to mobilize secretions from the nondependent areas of the chest to the central airways from where they may be suctioned. Vibration and percussion can be done mechanically as well. Vibration is generally used in neonates to avoid damage to their fragile chest walls.

Manual Hyperinflation: It is usually performed before and between suctioning to prevent hypoxemia while suctioning. The patient is disconnected from the ventilator and is bagged with a resuscitator bag using slow deep inspiration, inspiratory hold and quick release to enhance expiration. This causes the recruitment of atelectatic segments and also mobilizes secretions.

Continuous rotational therapy: This involves the use of specialized beds that continuously turn the patient along a longitudinal axis. It is currently unavailable in India.

Complications: Chest physiotherapy is associated with increased incidence of hemodynamic disturbances, higher incidences of gastro-esophageal reflux, elevation of intracranial pressure and increase in oxygen consumption. To some extent the effect on intracranial pressure and hemodynamics can be decreased by prior sedation and paralyzation of the patient. The head down positioning while doing rigorous physiotherapy is likely to increase the risk of aspiration and worsening of intracranial pressure. Neonates and children with fragile bones such as in rickets and osteogenesis imperfecta can develop rib fractures.

Currently there is very little data supporting the using of CPT for any condition other than atelectasis.

Humidification

Normally the upper airway of a person heats and humidifies the atmospheric air to body temperature and 100% relative humidity. Medical gases have no humidity and bypassing the upper airway as in patients with artificial airway such as endotracheal tube or tracheostomy makes humidification a must.Decrease in the humidity can lead to mucosal damage and tube occlusions, atelectasis, loss of FRC, hypoxia and increased incidence of pneumonia. Excessive humidification is also a problem and can decrease mucociliary clearance, cause hyper hydration and loss of surfactant activity. Humidification can be achieved using heated water humidifier (HW), heated wire or by Heat and Moisture Exchange (HME) filters. The appropriate temperature and humidity to be used in ventilated patients has not yet been established.

Heated Water Humidifier (HW): Heated humidifiers use heating elements to increase the temperature of water and humidity of the inspired gas(30). The degree of humidification of the inspired gas will depend on the temperature setting, flow rate, water level in the humidifier and the length of the circuit. These generally bubble the inspired gas through the column of water.These are to be used only with a high flow system such as that needed during mechanical ventilation. The temperature of the inspired gas has to be monitored in order to avoid over heating and tracheal burns.

Heated wire circuit: In an attempt to decrease the rainout associated with heated water humidifier, heated wire circuit is available. This is available in both reusable and disposable form. The temperature of the gas is maintained at a select value.

Heat and Moisture Exchangers: HME filters combine humidifying properties of plastic foam impregnated with hygroscopic substance, with bacterial filtering properties of filter membrane. HME filters are made of substances with low thermal conductivity such ceramic, polyurethane, polyethylene or cellulose sponge material. The hygroscopic substance can be Calcium Chloride, Magnesium Chloride, Aluminium Chloride or Lithium Chloride. It chemically absorbs water vapours in expired gas, which then saturates the inspired gas. HME has been found to provide safe and adequate humidification of inspired gases. Some of the filters available in the market claim to be 99.5% efficient in its filtration properties. A recently done study however casts doubts about this claim. Their use however is associated with lesser circuit contamination. There has not been any statistical difference in the incidence of ventilator associated pneumonia (VAP) with the use of HME filters. Its use can increase dead space and resistance, which may be overcome by increasing pressure support. It can be used safely up to a week or until visible liquid contamination occurs. This gets converted to cost saving on disposables, fewer need for breaking the circuit and hence reduction in bacterial contamination.

Aerosol Therapy

Aerosol is a group of particles suspended in air for a relatively long time. Aerosol therapy is used in order to deliver the drug directly to the site of action, there by minimizing the systemic side effects and improving the efficacy. The size of the aerosol is expressed as mass median aerodynamic diameter (MMAD). The MMAD determines the rapidity with which the aerosol will settle in the airway. Aerosol gets deposited through the process of impaction, sedimentation and diffusion. In order to be maximally effective the aerosol particles should be 0.5 – 5 µm in size. Particles larger than 3µm get impacted by its size on the tubing and endotracheal tube. Particles around 2µm get sedimented due to gravity and still smaller particles undergo diffusion.

Aerosol therapy may be provided using nebulizers or Meter dose inhalers (MDI). MDI's are as efficient and according to some studies more efficient than nebulizers. The latter however has a greater versatility and can be adapted to deliver various drugs.

An array of drugs like bronchodilators, steroids, antibiotics, anticholinergics, mucolytics, prostacyclin etc. gets delivered by the nebulizer route. The most common drug however is bronchodilator and steroids.

Characteristics of Aerosol generating device: Greater respiratory tract deposition occurs when the MMAD of the aerosol is in the range of 1-3 mm. The larger size particle can get impacted in the endotracheal tube and in the ventilator circuit. A nebulizer could have continuous or intermittent operation. Continuous operation requires the nebulizer to be driven by a pressurized gas source. Intermittent operation requires a separate line from the ventilator to drive the nebulizer during inspiration. Between the two, intermittent operation during inspiration is preferred as it lowers the wastage of drug.

Ventilatory Parameters: Adequate aerosol delivery is achieved in assisted modes of ventilation only if the patient is in synchrony with the ventilator. 20% more delivery can be achieved during CPAP mode than with volume cycled breaths . The tidal volume has to be higher than normal to compensate for the compressible volume of the tubing. Longer inspiratory time has to be used in order to increase the nebulizer generated aerosol to be inhaled with each breath. This is needed even in an MDI generated aerosol although the mechanism is not clearly known.

Circuit Characteristics: In general, smaller endotracheal tube, narrow internal diameter of the pediatric ventilatory circuit and humidification of gases all reduce the aerosol deposition in the lung. Lower density gas such as heliox mixture enable better deposition of the aerosol by decreasing the turbulence of air flow.

Position of the device: Aerosol delivery to the patient is improved by placement of a nebulizer at a distance of 30 cm from the endotracheal tube rather than between the patient wye and the endotracheal tube because the ventilator tubing acts as a spacer for the aerosol to accumulate between breaths.

Suggested method for delivery of drug by nebulization (modified from recommendations by Hess):

1. Clear secretions from endotracheal tube.
2. Ensure a high tidal volume to eliminate the dead space of the tubing.
3. Decrease the inspiratory flow rate such that the inspiratory time is prolonged.
4. Ensure 4-6 ml of volume in nebulizer and place the nebulizer in the inspiratory limb 30 cm from wye connection.
5. Ensure airflow of 6 lt/min to run nebulizer.

6. Nebulize solution only during inspiration.
7. Tap nebulizer intermittently during operation.
8. Disconnect nebulizer from the circuit after use.

Meter dose Inhaler (MDI): Only 1% of the content of MDI is the active drug. The rest is made up of propellants and preservatives. The amount of the drug delivered by MDI is much smaller than the nebulizer. MDI may be used directly on ET tube or through a chamber. A variety of chambers are available for use of MDI during Mechanical Ventilation. As a rule it is better to use a chamber device than to use MDI directly on the ET tube. The chamber could be collapsible or non collapsible and be attached to the inspiratory limb of the ventilator circuit. It is preferable to use a collapsible chamber that does not have to be disconnected from the circuit between uses. It is important that the actuation of the MDI is synchronized with the inspiratory time. An aerosol cloud enhancer spacer directs the fumes away from the patient into the spacer. The drug then gets carried to the patient during the inspiratory flow and this method of delivery is the most efficient.

Suggested method of aerosol delivery by MDI (modified from recommendations by Hess:

Steps 1-3 are the same as that for the nebulizer treatment

4. Place the acturator- spacer device in the inspiratory limb of ventilator
5. Shake the MDI and place on the spacer
6. Discharge MDI at the onset of inspiration
7. Repeat 20 to 30 seconds later

Of all the medicines used, bronchodilators are the ones that are most commonly delivered as an aerosol. Bronchodilators are used in an asthmatic. In order to reduce air trapping the ventilatory parameters one uses is almost exactly the opposite to the parameters that one has to use for optimization of aerosol delivery. Furthermore humidification is not possible while using aerosol. All this makes it difficult, wasteful and even harmful to use continuous aerosol therapy while on ventilator.

Endotracheal Suctioning

Suctioning can be done using the closed or open suctioning system. In closed suction system the suction catheter is encased in a plastic sleeve and is a part of the ventilatory tubing. The advantage of the closed suctioning system is that cost of disposable catheters is reduced; intuitively the risk of infection has to be less (although no published evidence). The PEEP effect is not lost while suctioning and hence the risk of hypoxemia in patients with reduced FRC is less. Its disadvantage is that resistance can be increased and it decreases the pulmonary bioavailability of β_2 agonist when used in asthmatics. In order to decrease the viscidity of secretion when not contraindicated, we increase the fluid administration to the patient – i.e. hyper hydrate the patient. In some institutions normal saline installation into the ET tube is routinely practiced. We use it only when the secretions are viscid and copious. While suctioning it is important to remember that mucosal injury can occur. Hence gentle suctioning taking care to not push the catheter up to the carina is a must.

Close suctioning system is now available for prevention of introduction of infection.

In PICU we use the open system except in ARDS where a close suctioning is required to prevent loss of PEEP and to prevent introduction of infection. (A variety of closed suction system brand that is commonly available is "STERICATH" available in infant, pediatric and adult sizes). In patients with pulmonary hypertension and elevated intracranial pressure, sedation prior to suctioning is a must as significant elevations of pressures and deterioration of hemodynamic parameters can occur.

Minimizing Drug Errors

Syringe pumps and infusion pumps are used for the accurate flow of fluids and for administering vasoactive drugs and sedative as well as muscle relaxant agents. Every nurse should learn how to use syringepumps accurately, as well as minimize errors of loading medications and dilution to deliver correct dose.

Nasogastric tube is inserted for suction/ nutrition.

Fluids and calories are supplied initially by the intravenous route. Type of fluid administered is determined by the general condition of the patient. Later nutrition is provided in a balanced formula given by nasogastric tube. Nasogastric tube is usually taped in place with care to prevent pressure on the nares. Most children have continuous feeding, but if bolus feedings are used, the tube is flushed with water after each feeding. Tubes are changed according to the padiatric intensive care unit policy. Nostrils are altered with each replacement to prevent nasal irritation and pressure. A strict intake and output chart should be maintained.

Accurate Intake and Output Chart

To maintain the accurate urine output chart a pediatric urine collecting bag or a urinary catheter can be inserted.

Skin care–
Daily sponge both with luke warm water and soap. Use transparent elastic film dressing to secure and protect central line and arterial line inserted site. Central lines and arterial lines should be changed every seven days(sometimes not possible due to technical difficulty in pediatric patients).

Routine measures for cleaning and maintaining skin integrity are an integral part of nursing care of the ventilated child. Skin fold require special attention to prevent excoriation. The child who is unable to move is prone to develop tissue breakdown and pressure necrosis, therefore, child may be placed on a pressure reducing or pressure relieving device to reduce pressure on prominent areas of the body.

Care of a patient with intracranial pressure monitoring

Intracranial Pressure (ICP) Monitoring

Principle In an infant before the closure of fontanels, if there is a situation of raised intracranial pressure, it first leads to a bulging fontanel, followed by gradual enlargement of head, as seen in patients with progressive hydrocephalus. However, after closure of fontenels, the skull is rigid (non-distensible). Therefore, any increase in the mass inside the skull (brain, cerebrospinal fluid, or blood) will produce an increase in ICP. After a critical level is exceeded, increases in ICP will produce damage to the brain by compressing it or by affecting the blood supply . The indication for ICP monitoring includes any acute neurologic deterioration where elevated ICP may produce further injury to the patient. Usually, acute traumatic events with a GCS less than 8 will require a monitoring device inserted either in the operating room or at the bedside in the PICU. The type of device and how it is inserted is usually the responsibility of the neurosurgeon placing the device. Ventriculostomy as well as intraparenchymal, subdural, or subarachnoid placement of catheters can be used. All but the intraparenchymal catheters are connected to the transducer via a fluid-filled tubing device. The ventriculostomy and the intraparenchymal fiberoptic devices are the most reliable and most used devices for monitoring ICP. A ventricular catheter allows one to not only measure ICP but also remove fluid if necessary, thereby providing a therapeutic option.

The intraparenchymal fiberoptic system provides for a very reliable method of ICP measurements, but does not permit the removal of cerebrospinal fluid (CSF). It is not a fluid-filled system but is easy to use.

The device is connected to a transducer and then to the monitor. A waveform with a numeric value is produced. The ICP should be less than 20cm H_2O. When monitoring ICP, it is imperative that the systemic arterial blood pressure be determined simultaneously. The difference between the mean arterial pressure and the ICP is the cerebral perfusion pressure. This should be more than 50cm H_2O in older patients and slightly less in younger children. The complications associated with ICP monitoring include bleeding (check coagulation factors before insertion), infection if left in for more than 5 days, injury to the brain parenchyma (usually only intraventricular catheters), and CSF leak (Fig. 10.4).

So, in summary three types of techniques are utilized to monitor ICP. The oldest one is the direct placement of a catheter into the ventricular system.

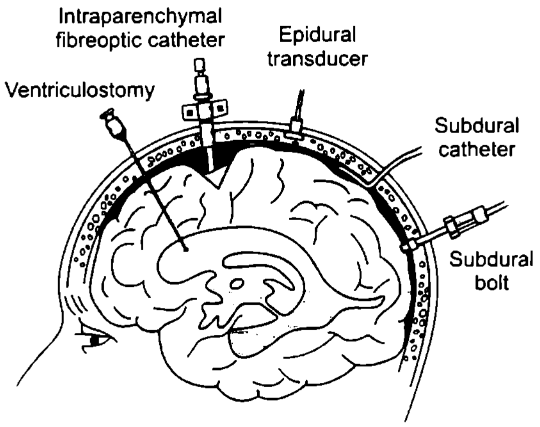

Fig. 10.4: Various devices to monitor ICP

This is the gold standard, but has greater risk of infection and is difficult to perform if ventricles are not dilated. Its major advantage is that CSF can be drained through this system to decrease ICP. The same principle can be used by placing a catheter in the epidural space (epidural catheter), but there are multiple sources of mistake or misinterpretation with it. The second system is a hollow bolt that is screwed into the skull until it reaches the subarachnoid/ subdural space (Richmond bolt). One of the problems with this system is that the bolts are prone to be inadvertently obstructed by brain tissue and give false readings. The system that is becoming more popular is a fiberoptics probe which can be placed in the brain (intraparenchymal), inside the ventricles, or in the subdural space (Camino Laboratories, San Diego, CA, USA). This device is accurate, and does not need recalibration, and is usually not affected by problems of obstruction.

ICP monitoring is particularly important for those patients who have lost the capability of autoregulating brain blood flow (e.g. severe head trauma). In this case, the cerebral perfusion pressure (CPP) is going to be directly dependent on the difference between mean arterial pressure and the intracranial pressure. When CPP is less than 40 mmHg, low cerebral perfusion can be expected. Aim should be to maintain CPP at least above 50 to 60 mmHg depending upon the age of the child. It is important to remember that MAP is measured at the level of the right atrium, but the driving pressure for CPP is the MAP at the level of the carotid artery entering the brain. Therefore, if the head is elevated above the level of the right atrium (where the MAP is measured), the height difference should be subtracted from the measured MAP (1 cm = 0.7 mmHg). This type of monitoring is helpful when there are intracranial masses, and for the monitoring of ICP secondary to vasogenic edema (e.g. meningitis). The value of using an ICP monitor after cyto-toxic edema (e.g. near drowning, hypoxic encephalopathy) is highly controversial. A newer method currently being tested, use a transducer placed at the level of the anterior fontanel reflective of ICP. This technology needs precise calibration, familiarization with the equipment, and an open fontanel.

Dealing with Visitation and Families

Visitors are not routinely allowed in the PICU except the mother or the father, only one visitor is allowed at a particular time. With non-ventilated patient one attendant can be allowed. Visitors are instructed strictly to wash hands before and after contact with the patient. At the time of doctors rounds, parents are called for post rounds counselling and communication regarding patient condition, progress and plan for the day.

Communication with the Families

Nurses spend more time with patients and families facing the end of life than any other health professionals. Nurses are intimately involved in all aspects of end-of-life care and they address the myriad of needs facing individuals at this time of life. Expert nursing care has the potential to greatly reduce the burden and distress of those facing life's end and the ability to offer support for the many physical, psychological, social, and spiritual needs of patients and their families. Nurses, individually and collectively, have over the past decades demonstrated commitment to end-of-life care.

Unfortunately, research in previous years has demonstrated that major deficiencies exist in nursing education for end-of-life care. From 1997 to 2000, researchers at the City of Hope National Medical Center conducted a project titled, "Strengthening Nursing Education to Improve End-of-Life Care" supported by The Robert Wood Johnson Foundation. The research conducted during the course of this project demonstrated major deficiencies including the gross lack of content in nursing texts in end-of-life care, minimal content with the nursing curriculum, reported inadequacy of nursing faculty knowledge related to end-of-life content, and many other educational barriers that impede nursing practice. Results from other pivotal studies conducted nationwide came to the same conclusion - nurses simply were not prepared to provide optimum end-of-life care.

In the following section the discussion pertains to nursing communication with the families of a critically ill child admitted to the PICU, who is at risk of dying, or is refractory to all treatment modalities with imminent mortality.

Routinely it is a good idea for the nurse to be present during rounds and physician family communication meetings to discuss diagnosis, prognosis, clinical condition, any changes in treatment, response to treatment, anticipated surgery or change in therapy, any new consultations.

Informed Consent

*Legal term meaning willing acceptance of an intervention after full description of the intervention
*Exercised as "permission" by parents or guardians for incompetent minors
Legal considerations in withdrawing treatment

In the United states

Under the *Child Abuse Prevention and Treatment and Adoption Reform Act (1985)*, withdrawal is permitted when treatment:
*merely prolongs dying
*is "not effective in ameliorating or correcting all the infant's life-threatening conditions"
*is otherwise futile in terms of survival
Other applicable terminology

Do Not Attempt Resuscitation (DNR)

Medical Futility

Agreed on goal of treatment
A means identified for achieving that goal
Virtual certainty the means will not achieve the agreed on goal

Assisted Suicide

"When a person other than the patient provides a means (usually a medication) to a patient with the knowledge that the patient will use the means to commit suicide."

Euthanasia

"Deliberately intending to cause a patient's death, either by administering a lethal agent or by withdrawing a means that represents a reasonable hope of benefit and is not too burdensome."

In India

There is **no such legal provision to discontinue therapy (withdrawl) or withholding** even if it is considered futile in a brain dead patient. **Do not resuscitate status option does not exist.**
Therefore in our scenario non escalation strategy is used. Not adding any newer therapeutic modalities once the treatment is considered futile.
Let nature take its course with a continued treatment in PICU.
Assisted suicide and euthanasia are illegal in INDIA.

Some of the families would take patients home LAMA (leaving against medical advice) when they recognize that the death is imminent or the treatment is futile. This is hastened in private hospitals by escalating medical bills with no definite benefit in sight.
Most of such decisions are made as joint family, physician.

It is still not a routine to involve nurses in these decisions although it is extremely important as an active team member, the nurse be involved in such meetings.

Following discussion pertains to nursing responsibility as it applies to the PICU patients and families:

Breaking Bad News: The Nurse's Role (for Pediatrics)

Inform family of need to discuss important information.

Provide an opportunity for supportive friends or family to be present when the information is shared. Tell the news in a private setting, with the physician, nurse, and social worker present. Bring the family (generally parents without the child first, depending on the relationship and preferences) to a private room. If appropriate and desired by the family, assist them in telling their children (patient and siblings) afterwards.

Sit down near the family, not across a table. Do not stand. Look at the family members in the eye (if culturally appropriate) to engender trust. Ask them to tell you about their child and about any consistent values of the child and about the things that give him or her pleasure. Ask how much they want to know about his or her medical condition and prognosis. Ask them what they understand is happening. Clarify misconceptions, ask the family to explain what they understood was said. Then, solicit additional questions.

Be unhurried. Don't look at your watch. Ideally, members of the interdisciplinary team participate as full members during the family conference. Bring trainees to the family meeting. It keeps trainees informed so that unnecessary and often damaging miscommunications do not occur. However, do not overwhelm the family with white coats- have trainees take turns in attending family meetings.

Be specific. The physician should present the options, including a description of life-sustaining treatments, the child's current status, the chance of survival, the probability of full recovery (and the probability of significant disability), and the possible effects of the child's long-term survival on the family. Be sure to explain the benefits and burdens (including prolongation of suffering) of each potential care plan, the potential reversibility or irreversibility of the conditions being treated, the time frame of reevaluation, the projected future quality of life, and the comfort measures available if the ICU interventions are curtailed or discontinued. Give reassurances that, if life-sustaining medical interventions are discontinued, the child will continue to receive attentive care for the relief of symptoms; describe the procedures to be undertaken, including the opportunities to observe important customs and rituals and the visitation allowances.

Helping Parents Face the Death of their Child

Communication

Listen attentively.
Find out what the family knows and what they want to know.
Use language that family members can understand.
Call the child by name.
Use silence as an ally but watch for signs that parents need to talk.
Encourage questions.
Do not offer platitudes.
Do not automatically offer tissues.

Facilitate Family Grieving

Offer a private place for the family to retreat.
If death occurs, allow the family time with the child after the death.
Encourage involvement of siblings.
Preserve memories of the child: last height, weight, lock of hair, hospital name band, plaster of Paris hand-or footprint, picture of the child, child's blanket and clothes in a plastic bag (to preserve scent).
Help establish links with a social worker, spiritual support person (chaplain, priest, rabbi, healer), funeral director.
Provide specific information about how the needs of siblings can be met.
Provide pamphlets for family members and friends to give them tips about how to help the parents.

Team Approach

Doctor, nurse, dietician, physiotherapist, child, family, social worker, ward secretary and other staff works as a team. Terminally ill children and their families may require different kinds of assistance at different times. They face many problems that are non-medical in nature. Team members may support one another. To be effective team members, nurses must communicate, collaborate, and co-operate with other members of the team.

Accept responsibility for their contribution to the plan of care and be accountable for the outcome.

Provide emotional support to the parents following the death of the child.

Allow families who wish it the opportunity to spend sometime alone with the child after death.

Provide privacy for parents to express their grief in whatever manner they choose.

Be aware that your compassionate silence may be most helpful to families than small talk.

Assist families to contact other relatives. Anger reactions should be dealt with composure and assistance from hospital security should be readily obtained as necessary.

Make certain that families have a safe and comfortable means to get home.

SUMMARY

Best outcome is achieved by team approach. Nursing care remains the pillar on which the whole PICU rests. Outcome depends on overall quality of hospital care including the quality and compassion of medical and non-medical team. Nursing service should never underestimate the nursing contribution, therefore nursing care should always be provided whole heartedly.

APPENDIX
COMMONLY DONE PICU NURSING PROCEDURES AND POLICIES

1. OXYGEN THERAPY

Definition

Oxygen therapy is Administration of oxygen at a concentration greater than that found in the atmospheric air

Purpose

1. To prevent hypoxemia by adequate transport of oxygen in blood in patients with pulmonary diseases
2. Provide adequate tissue oxygenation for problems associated with
3. Reduced oxygen carrying capacity of blood
4. Decreased cardiac output
5. Hypoventilation
6. Increased metabolism

Articles

1. Oxygen setup including -
2. Oxygen flow meter and humidifier with sterile water
3. Oxygen delivery device – Nasal cannula, nasal catheter or facemask

Methods of Oxygen Administration

Oxygen by Nasal cannula: The soft nasal Cannulae are inserted into nostrils and held in place by adhesive tape.

Oxygen by mask: The mask should be well fitting and cover the nose and mouth of the patient. Three types of masks are available.

1. Simple Mask
2. Venturi Mask
3. Partial rebreathing Bag

Oxygen by Tent: It consists of a canopy over the patient's bed that may cover the patient fully or partially and is connected to oxygen supply.

Special Points to Remember

Patients may develop infection, atelectasis, Oxygen induced apnea, retrolental fibroplasias, asphyxia, as complications which should be prevented.

Oxygen source can be oxygen cylinder or centralized oxygen supply or wall outlet.

Factors helping in prevention of fire during O_2 administration

1. Properly ground all electrical plugs and electrical equipments in the area.
2. Do not permit use of spark producing electrical appliances.
3. No smoking.
4. Never use oil on the oxygen equipment.

Humidification

As oxygen and other compressed gases are dry (contains n water vapor) humidity is added before inhalation of the ga Humidifiers are devices that add water vapor to inspired g to decrease drying effect of the gas. Bubbling the O_2 throug water should humidify oxygen administration. The water ma be at room temperature.

Advantages of Humidification

Prevents drying and irritation of respiratory mucou membranes.

1. Prevents drying and thickening of respiratory tra secretions.
2. Loosens secretions.

Procedure

Receive the order of doctor.
Check the source of oxygen supply.
Wash hands.
Explain the procedure and provide privacy.
Turn on the flow regulator and check the free flow of gas.
Apply the device as decided.
Supply the rate as per the order.
Make the child comfortable.
Assess the child's response to the therapy.
Monitor oxygen saturation, Respiratory rate, and ABG required.
Document in Critical Care Flow Sheet and Nurses notes.

2. BLOOD TRANSFUSION

Definition

It is administration of whole blood or its components such a blood cells and plasma through the vein into the body.

Purpose

1. To increase the blood volume after a haemorrage, surger burns
2. To counteract diseases of blood
3. To correct blood deficiencies like anemia
4. To provide antibodies

General Instructions

1. Maintain aseptic technique through out the procedur
2. **Check the labels on blood and ensure that appropriat patient gets it**
3. Use a large cannula to transfuse
4. A blood transfusion set with a filter should be used t prevent clots from entering the blood

5. Record the time of starting and discontinuing transfusion
6. Monitor vital signs before, during and after the transfusion
7. Refrigerate the blood if not used within 30 minutes and bring to the room temperature before the transfusion
8. Observe the patient for any complaints of dyspnea, urticaria, nausea, vomiting, or chills
9. Stay with the patient for the first 10 minutes of transfusion to monitor vital signs and any sign of allergy or reaction. Infusion should be continuous usually no more than 4 hours and if it stops in between, correct immediately
10. If there is any sign of reaction, stop and notify the physician, save the blood and tubing and send to laboratory
11. Observe the site for leaking and swelling
12. No medication to be added to blood
13. If IV fluid has to be continued soon after the transfusion, run the tubing with normal saline till the whole tubing is clean and then put I.V. infusion

Articles Required

A tray Containing
1. Spirit
2. Betadine
3. Tr.Benzoin
4. Tourniquet
5. Sterile blood transfusion set with filter
6. Large needle
7. Elastoplast
8. Sterile gloves
9. Normal Saline
10. Medications to treat allergic reaction: such as chlorphenaramine, epinephrine, hydrocortisone

Special Points to Remember

Look for the following complications which can occur in the patient receiving blood transfusion
1. Circulatory overloading manifested by dyspnea, sudden anxiety, Orthopnea, coughing of pink frothing sputum
2. Febrile or pyrogenic reactions manifested by fever
3. Allergic reactions manifested by urticaria, itching, wheezing, anaphylaxis

3. ELECTROCARDIOGRAM (ECG)

PICU nurse should know how to do an ECG.

The electrocardiogram is a graph of the electrical impulses from the heart. ECG is painless non-invasive test and usually takes about 10 minutes to complete the procedure. The procedure involves placing 3 to 12 leads on the person's chest and on certain peripheral pulse site. The electrodes are attached by leads to the electrocardiograph.

Each heart beat is the result of an electrical impulse which originates in the sino-atrial (SA node) of the right atrium and is conducted through a network of fibres within the heart and causes the heart to contract. This same electrical impulse i spread outwards from the heart to the skin, where it can b detected by electrodes attached to the skin. Thus ECG or EK is a display of the electric action of the heart.

There are several types of ECG. Continuous monitorin can be done by cardiac monitor. The improper placement c the chest leads can greatly alter the tracing and diagnosis.

Placement of Chest Leads

V_1 In the IVth intercostals space to the right of the sternur
V_2 In the IVth intercostals space to the left of the sternur
V_3 Midway between V_2 and V_4.
V_4 In the Vth intercostals space in the mid clavicular lin on the left side.
V_5 In the same horizontal position as V_4 in the anterio axillary line, on the left side.
V_6 In the same horizontal position as V_4 in the axillary lin on the left side.

Objectives

- To assess the cardiac status of the child.
- To know the infection of heart muscle
- To confirm the diagnosis.
- To evaluate the treatment in heart patients
- To keep continuous watch and monitoring over the hea rhythm.

Nursing Intervention

Primary Phase

1. No special preparation is needed.
2. Explain the procedure to the patient/child.
3. Remove the ornaments. Provide gown or loose uppe clothing.
4. Tell the parent/child that the test is painless and non invasive.
5. Keep attendant away from the child only during th procedure. Touching can alter the results.
6. Assess the vital signs (TPR and BP) for baseline data.
7. Drape the chest properly, if patient is female.

Performance Phase

1. Place the child in a supine position.
2. Clean the skin with alcohol wipe/ spirit swabs, wher the leads are to be applied.
3. Apply leads using pre-jelled disk or ECG paste.
4. Switch on the ECG machine.
5. Enter patient data (name, age, date etc)
6. ECG Technician/ Physician/ Nurse records the ECG.

Final Phase

1. Switch off the machine.
2. Remove leads.
3. Clean ECG paste from the skin.

4. Physician/intensivist/cardiologist interprets the ECG.
5. If the parent is anxious about the test, explain the results after obtaining permission from the consultant or have them in touch with the consultant.

4. SECURING AND CARE OF ENDOTRACHEAL TUBES (ETT'S)

Standards

1. Assigned nurses and intensivist may secure and care for endotracheal tubes. Two people are required for this procedure.
2. The endotracheal tube will be secured in such a way as to maintain its desired position.
3. The cuff pressure of an endotracheal tube will be checked once a shift and prn.
4. The endotracheal tube will be secured in such a way as to prevent pressure sores from developing.
5. The endotracheal tube will be secured so as not to occlude the tube.

Outcomes

The patient will not develop problems with pressure sores from securing an ETT. The ETT will not become malpositioned.

Equipment

1. Elastoplast(Dynaplast) or tape
2. Solvent ether
3. Tincture Benzoin

Procedure

1. Once the ETT is placed in the patient and position is checked by auscultation the ETT is secured in using tape.
2. Tape is then prepared by cutting two pieces cutting each to form trouser leg shape.
3. The tape is applied so as main body of tape sits on cheeks and the bifurcation sits at the corner of the mouth. One leg of each tape is secured around tube and one leg is taped to either the top or bottom of each lip.
4. The tube is to be anchored to both top and bottom lips to ensure good security.
5. A chest x-ray should be attended to check on position of ETT and the distance of the tube at the patient's lips.
   An additional piece of tape can be placed over the tape and under the lower lip to give added security.

Post Procedure

Note tube distance at patient's lips on the patient's Critical care flow sheet

Special Precautions

1. Strict aseptic technique to be followed for the entire procedure
2. A chest x-ray should be attended to check on position o ETT and the distance of the tube at the patient's lips
3. Take a second person to help you for the entire procedur
4. The cuff of an endotracheal tube will be checked once shift and prn.
5. Check for any dislodgement at every time
6. Do not mute the alarm or put off the alarm

5. DRAWING ABG'S FOR BLOOD GAS ANALYSIS

Policy

Nurses working in the PICU area may collect arterial sample from arterial lines if familiar with the management of arteria lines.

- Radial puncture should only be attempted by experience Nurses familiar with or experienced in technique, or unde supervision of same persons.
- Goals to be achieved are to obtain accurate and satisfactor sample without undue stress or discomfort for patient.
- Prevention of contamination into arterial infusion/ monitoring set
- Minimize possible risk of haematoma formation.

Outcomes

- Maintenance of patient safety.
- Prevention of introduced infection in the critically ill child

Procedure

- Wash hands prior to collection sample.
- Assemble equipment; blood gas syringe, swabs, 5ml syringe, gauze to evacuate blood line onto.
- Swab area on and around port.
- Remove cap.
- Attach syringe and openline to air.
- Draw off line fluid and initial blood - approximately 3mls.
- Draw off sample.
- Close stop cock to air.
- Remove sample syringe.
  Blood can be given back
- Flush line.
  Close stop cock to air.
- Replace port cap.

Special Considerations

- Sample should be taken to gas analysis machine at earliest possible moment, as results may be altered. There should be no air bubbles.
- Agitate sample between palms of hands to mix blood and syringe content well prior to putting sample into machine.
- Samples that are being sent to the lab need to be transported on ice to prevent deterioration.
- Ensure correct labeling information is on blood sampling and form.

6. GUIDELINES FOR BLOOD CULTURE COLLECTION

Indications

Routine blood cultures should be performed on any child in whom there is a suspicion of bacteremia or candidemia.

Timing

Blood cultures should be drawn prior to the institution of antibiotics whenever possible. If empiric treatment is an emergency, blood cultures should still be drawn as soon as possible after institution of antibiotics.

Volume of Blood Per Set

In pediatric age group 2-3 ml of blood should be enough

Number of Sets of Blood Cultures

Single sets should not be used to evaluate any patient with suspected bacteremia or candidemia. The optimal yield is obtained with two or three sets of blood cultures.

No more than three blood cultures should be obtained for any given 24 hour period.

Site of Blood Culture

Blood should be obtained from peripheral venous or arterial sites.

The practice of drawing blood for culture from catheters or the groin should not be routinely performed when a peripheral (i.e., non-catheterized) site is available.

Labeling

Labeling the site of each set of blood cultures, particularly regarding whether a set was drawn from a catheter, the groin, or not, is of utmost importance in helping to distinguish pathogens from contaminants in those cases in which no peripheral access can be found.

PREPARATION OF THE SITE FOR CULTURE

1. After the vessel site is selected, a 5 cm area of skin should be disinfected by swabbing concentrically with 70% alcohol, from the venipuncture site outward.
2. The site should be cleansed once again, this time with 10% povidone-iodine or 2% tincture of iodine again in a circular motion.
3. Allow the iodine to dry completely before performing venipuncture. This should take 1 - 2 minutes.
4. While waiting for the site to dry, the plastic cap covering each blood culture bottle should be removed, and the rubber stopper should be decontaminated with 70% alcohol. (Iodine solutions will disintegrate the rubber and should not be used.)
5. 2-3 ml of blood should be withdrawn from the puncture site.
6. Do not change needles between venipuncture and inoculation of the bottles, or between bottles. The risk of needlestick is increased, while the chance of contamination is not significantly lessened.
7. Remove the iodine solution from the skin with alcohol. This will minimize the possibility of hypersensitivity.

7. CARE OF A PATIENT WITH CENTRAL LINE

A central line is inserted for administering maintenance fluid, sedation, muscle relaxant and inotropic support and for central venous pressure (CVP) monitoring.

A. Procedure: Central Venous Catheters

2. *Management protocol*: (applies to all types of CVC):

a. Types:
   Single, double and triple lumen catheters are placed. 4fr double lumen, 5.5 french triple lumen 8cm and 16cm are available. In older patients 7 french catheters are also available

b. Sites:
   - i. Ideally Subclavian is the preferred site for routine stable patients(risk of pneumothorax), followed by internal jugular site .
   - ii. In pediatric Femoral access is preferable where:
     - Limited IV access (burns, multiple previous CVC's),
     - Thoracic approach is considered hazardous:
       1. Severe respiratory failure from any cause ($PaO_2/FiO_2 < 150$)
       2. Hyper expanded lung fields (severe asthma, bullous lung disease)
       3. Coagulopathy (see below)
     - Inexperienced staff requiring urgent access, where supervision is not immediately available.

c. Coagulopathic patients:
   - i. INR > 2.0 or APTT > 50s → correct with FFP
   - ii. Platelets < 50,000 → transfuse 1 pack (5u) platelets
   - iii. Failure to increase platelet count after transfusion → avoid subclavian
   - iv. Uncontrolled coagulopathy → use femoral approach or PICC

d. Technique policy:Assist the intensivist in central line insertion
   - Local anaesthesia in awake older children patients,but mostly sedation is required.
   - Strict aseptic technique at insertion:

Need central line kit, dressing tray, betadine spirit, heparinized saline, syringe, gauze, suture kit 2.0 and 3.0 silk

a. Hand disinfection: surgical scrub with chlorhexidine for >1 minute

b. Sterile barrier: gown, glove, cap and mask and sterile drapes.

c. Skin prep: chlorhexidine 1% / 75% alcohol
   - Seldinger technique only.
   - Suture all lines
   - Dressing: non occlusive dressing

- Flush all lumens with heparinised saline
- Check CXR prior to use.

e. Maintenance: Dressing every day.
  - i. Routine change of site at 7 days. Patients with difficult access, routine change may not be indicated.
  - ii. Daily inspection of the insertion site and clinical examination for infection irrespective of duration of insertion.
  - iii. Catheters are left in place as long as clinically indicated and changed when:
    - Evidence of systemic infection
      - New, unexplained fever
      - Unexplained rise in WBC
      - Deterioration in organ function
      - Positive blood culture by venipuncture with likely organisms (S. epidermidis, candida spp.), and/or
    - Evidence of local infection - inflammation or pus at the insertion site
  - iv. Guidewire exchanges are actively discouraged. They may be indicated in the following situations, after discussion with a Consultant:
    - a. Mechanical problems in a new catheter (leaks or kinks)
    - b. Difficult or limited central access (eg burns).
  - v. Maintenance of lumen patency
    - a. Central venous catheters
      - Flush unused lumens with 1ml heparinized saline (1u/ml) 8 hourly

3. Complications:
  - a. At insertion
    - i. Arterial puncture
      - a. Haematoma with mass effect
      - b. Arterial thrombosis/embolism
    - ii. Pneumothorax, haemothorax, chylothorax
    - iii. Neural injury (phrenic, brachial plexus, femoral).
  - b. Passage of wire/catheter
    - i. Arrhythmias
    - ii. Perforation of SVC, RA; tamponade
  - c. Presence of catheter
    - i. Catheter infection: rates increase under the following conditions:
      - Size of catheter - thicker catheters (pulmonary artery catheters)
      - Vascaths
      - Site of catheter - femoral > internal jugular > subclavian sites
      - Number of lumens
      - Nature of fluid through catheters - TPN or dextrose solutions
    - ii. Thrombosis
    - iii. Catheter/Air embolism
  - iv. Knotting of catheters (esp PAC)
  - v. Pulmonary infarct / arterial rupture (PAC)
  - vi. HITS secondary to heparin.

NB: Where insertion of a CVC presents "significant risk" in a non-urgent situation, consider insertion of a PICC line as an alternative.

B. HEPARIN LOCK FOR CENTRAL VENOUS CATHETER LINES

Policy

- Management of care of central venous catheters (CVC) may only be undertaken by Nurses undergone training to give intravenous medication.
- Central Venous Catheters lumen extension (pigtail) must be heparin locked when not in use, or after each intermittent medication, to ensure patency.
- Procedure should be carried out every forty-eight hours unless line is already assessed.
- Procedure must be carried out under strict asepsis.

Outcomes

- The patient will experience no infection through contamination of the CVC line during his/her stay at the Hospital.

Equipment

- Sterile dressing pack 2 10-x10cm sterile gauze packs
- IV solution, as ordered
- Chlorhexidine solution
- 1 pair sterile gloves, Rubbish bin
- Yellow luer lock cap one per pigtail Heparin flush (sodium heparin 50u/50mls) per pigtail
- 2 × 5ml syringes per pigtail
- 1 × 1ml syringe per pigtail
- Sodium Heparin 10 unit/ml 2ml every 8 hourly or before and after discontinuation for drug administration.

C. CENTRAL VENOUS CATHETER SITE DRESSING

Policy

Management and care of Central Venous Catheters (CVC) may only be undertaken by Registered Nurses accredited to give intravenous medication and Registered Nurses accredited to give intravenous medication may undertake training to care for CVC.

Central Venous Catheter dressings must be changed at least every 72 hours or when dressing becomes soiled.

Area around catheter insertion site will remain free from any signs or symptoms of possible infections.

Area around catheter insertion site will remain aseptic to decrease chances of possible infection.

Any sign of infection or possible infection will be reported to the Physician for assessment at the earliest possible moment.

Outcomes

The area around the catheter insertion site is to remain infection free during the hospital stay of the patient.

If infection does occur, arrangement must be made with the Physician for earliest possible site change to be carried out.

Special Considerations

Patients with long term Central Catheters in place may carry out the procedures they are familiar with under supervision of a qualified Nurse from hospital.

While in hospital, management of the Central Line by the patient must meet the standards set down by hospital.

Equipment

- Dressing pack x 1 Hansapor (wound dressing) 15 cm × 8 cm × 1
- Betadine solution
- Rubbish bin

Procedure

- Explain procedure to child/parent prior to commencement.
- Aseptic preparation prior to commencing procedure.
- Prepare dressing pack at bedside prior to positioning patient.
- Place patient in supine position.
- Remove old dressing and check site for discomfort, redness, inflammation and/ or leakage of fluids from around insertion site.
- Clean area around insertion site with Betadine solution, allow area to dry before applying dressing.
- Label dressing with time and date of change.
- Record date and time of dressing change on flow chart.
- Note in patient's chart condition of insertion site and inform intensivist of signs of infection.

D. DRAWING BLOOD FROM A CENTRAL VENOUS CATHETER

Policy

Management and care of Central Venous Catheters (CVC) may only be undertaken by nurses undergone training to give intravenous medication.

Procedure should be carried out under strict asepsis.

To have a uniform approach to drawing blood from a Central Venous Catheters by trained nursing staff.

The Central Venous Catheters is not an ideal site for drawing blood samples but may be used in conditions where other access is not available.

Caution is to be taken when aspirating blood samples from the Central Venous Catheters not to hemolyse sample.

Rapid withdrawal can create a vacuum which may damage/collapse catheter or blood vessel.

Caution is to be taken not to contaminate blood sample with solution infusing through other ports.

Proximal port on the Central Venous Catheter should be designated for drawing blood and kept Heparinized for this reason.

Outcomes

The patient will experience no infection through contamination of the Central Venous Catheters during his/ her stay at hospital.

Blood samples drawn from the Central Venous Catheters will not be contaminated by other solutions being infused through other ports of the same Central Venous Catheter.

No damage will occur to either the blood vessels or the Central Venous Catheters through excessive force while drawing blood.

Equipment

Equipment as for Heparinizing Central Venous Catheter
Eye protection
Apron
Yellow Vacutainer Shield
Vacutainer luer lock
Appropriate blood collection tubes.

Procedures

Explain procedure to patient prior to commencement.

Aseptic preparation prior to commencing procedure.

Maintain proper barrier protection to protect nurse against possible blood contamination; prepare dressing pack at patients bed side.

Place patient in supine position. Have patient turn head away from Central Venous Catheters site during procedure.

Turn off infusion at least one minute prior to sampling.

After removing 5 mls of blood from CVC pigtail attached syringe and remove required amount of blood for blood test. Draw off blood for electrolytes and full blood counts prior to coagulation studies.

If coagulation studies are the only tests required it may be necessary to draw up to 10 mls of blood for discard prior to drawing sample blood.

Re-heparinize CVC port following Policy and Procedure for 'Heparin Lock for Central Venous Catheter Lines'.

Record date and time of procedure on flow chart.

Note in patients chart procedure carried out and any problems noted during procedure.

E. REMOVAL OF CENTRAL VENOUS LINE STANDARDS

Policy

- Management and care of CVC may be undertaken by a registered nurse accredited to give intravenous medication.
- Upon removal of the CVC, Universal precautions must be maintained to avoid contamination of the health care worker through exposure to blood borne pathogens.
- Aseptic technique is used at the insertion site to decrease chances of infection to the patient.
- Dressing is to remain in place 24-72 hours according to length of time that catheter was in place.

- Observe patient post removal for the following i.e S and S of bleeding, air embolism or infection of at the site.

Outcomes

- The patient will experience no infection through contamination of the CVC site during his or her stay in Hospital.

Equipment

- Sterile dressing pack Air occlusive dressing i.e. tela gauze with antimicrobial ointment
- Hibitane solution one pair sterile gloves
- Rubbish bin, Sterile jar to collect catheter tip if infection is suspected
- Stitch cutter for removing sutures, Sterile scissors

Procedure

- Explain the procedure to the patient prior to procedure.
- Aseptic preparation prior to commencing procedure.
- Prepare dressing pack at bedside prior to positioning patient.
- Turn off all infusions
- Place patient in Trendelburg or supine position.
- Instruct patient to preform Valsalva maneuver or to hold breath on command.
- If tip of catheter to be sent for cultures have sterile equipment ready.
- If tip to be cultured prep skin around site with aseptic solution and remove catheter at 90 degree angle
- Remove suture holding in CVC while insuring CVC does not accidently migrate out. Ensure all suture material has been removed.
- As catheter is removed ask patient to preform Valsalva maneuver or to hold breath.
- Immediately cover area with sterile gauze to apply pressure to area.
- Cover the site with occlusive dressing while patient is still reforming Valsalva maneuver.
- Reposition patient.
- Chart that central line has been removed time, date and condition of catheter. Chart type of catheter removed. Chart condition of patients skin i.e. swelling, redness or discharge.

8. ARTERIAL PRESSURE MONITORING

Because of the technical limitations of non-invasive monitoring, invasive hemodynamic monitoring may be preferred. Sites commonly used to place catheters in an artery for invasive monitoring include the radial, ulnar, posterior tibial, and dorsalis pedis arteries. Less frequently used are the femoral, axillary and brachial arteries and, when available, the umbilical artery. Arterial lines may be inserted either percutaneously or via cutdown if one is unsuccessful with percutaneous attempts. Before attempting to insert an arterial line one should ensure that collateral circulation exists if possible by performing an Allen test (for radial or ulnar lines). Once the catheter is properly inserted, a pressure transducer and pressure tubing are used to connect the catheter to the monitor. A continuous pressure waveform tracing can then be displayed on the monitor screen and should be displayed along with the simultaneous ECG tracing.

Principle Mechanical energy (the pressure that blood exerts on a transducer dome) is transformed into an electrical signal, it provides easy access to monitor arterial blood samples. Heparinized saline (1 unit of heparin/ml of saline) is used to flush the angiocatheter system continuously at 2 to 3 ml/hr to maintain patency and good arterial waveform display.

It is important to remember that because impedance increases in arteries distal to the aorta, a waveform with a higher spike will be seen in a peripheral artery than in a more central artery. This will produce a higher systolic pressure distally, but the mean arterial pressure (MAP) will not be affected. Mean arterial pressure is the driving pressure to perfuse the brain, the coronary arteries, the kidney, and the splanchnic bed; therefore, it is the measurement most often monitored in the PICU. The arterial waveform may be helpful in diagnosing hypovolemia (very narrowed and blunted dicrotic notch), determining the severity of cardiac dysrhythmias (pulsus alternans), and evaluating the effects of respirations (air trapping) or high pericardial pressure on blood pressure (pulsus paradoxus). Arterial lines also allow for the frequent sampling of blood for various laboratory tests including arterial blood gases, electrolytes, coagulation panels, and others as needed.

A. ARTERIAL LINE PLACEMENT

An arterial line is inserted for the frequent blood gas analysis and continuous arterial blood pressure monitoring.

Procedure

1. *Indications*:
   a. Routine measurement of systemic blood pressure in PICU
   b. Multiple blood gas and laboratory analysis
   c. Measurement of BP during transport of patients in hostile environments (e.g. during retrieval)
2. *Management protocol:*
   a. Remove and replace lines inserted in unsterile conditions as soon as possible.
   b. Brachial and femoral arterial lines must be changed as soon as radial or dorsalis pedis arteries are available.
   c. Aseptic technique:
      i. clinical hand wash with chlorhexidine/alcohol + gloves.
      ii. skin prep. with chlorhexidine 1%/75% alcohol
   d. Local anesthesia in awake patients
   e. Cannulae :
      i. Arrow (Seldinger technique): radial or femoral kits.
      ii. 22-24 G cannula
      iii. Single lumen 22G CVC for femoral arterial lines.

   f. Sites: (order of preference): radial, dorsalis pedis, ulnar, brachial, femoral.
   g. The femoral artery may be the sole option in the acutely shocked patient.
   h. Dressing: occlusive + sutured
      i. There is no optimal time for an arterial line to be removed or changed.
   j. IA Cannulae are changed/removed only in the following settings
      i. Distal ischaemia
      ii. Mechanical failure (over damped waveform, inability to aspirate blood)
      iii. Evidence of unexplained systemic or local infection (cf CVC lines)
      iv. Invasive pressure measurement or frequent blood sampling is no longer necessary.
   k. Measurement of pressure:
      i. Transducers should be 'zeroed' to the mid-axillary line.
   l. Maintenance of lumen patency
      i. Continuous pressurized heparinized saline flush (1 u/ml) at 3 ml/hr.
3. *Complications:*
   a. Infection
   b. Thrombosis
   c. Digital ischaemia
   d. Vessel damage/aneurysm
   e. HITS (secondary to heparin infusion)

Procedure: Insertion of an Arterial Line

Policy

- Insertion of an Arterial Line is performed by the Intensivist in the Intensive Care Setting where haemodynamic monitoring equipment is available.
- Nurse present during procedure to set up and maintain sterile field, assist with procedure and to set up pressure lines for haemodynamic monitoring.
- Arterial Lines are used for the frequent access for arterial blood sampling and intra-arterial pressure monitoring.
- The nurse will set up and maintain a working sterile field for the Intensivist to perform procedure.
- The procedure will be performed under the strictest aseptic conditions.
- The procedure will be explained to the patient (where applicable) or the patients family, and written consent will be obtained by the medical officer.
- Universal precautions will be maintained throughout the procedure and in the clean up phase post procedure.
- Patient safety and comfort is maintained throughout the procedure.
- Immediately post insertion and at frequent intervals during placement of the arterial line the affect limb will be observed for bleeding from around insertion site. Circulation and colour as collateral circulation of the affected limb will be checked.
- Any circulatory problems arising from the placement of the arterial line will be immediately reported to the Intensivist.

Outcomes

- The risk of infection will be minimised through maintaining a sterile field for Intensivist to work in.
- The catheter will be located in the Radial Artery/ Femoral Artery, right or left.
- The risk of infection will be minimised through the use of strict aseptic technique.
- There will be no circulatory damage to the affected, limb due to placement of the Arterial Line during patients stay in Hospital.

Equipment

- 500 mls Heparinize Normal Saline (premixed)
- Pressure Bag
- 2 /0 black silk on a straight cutting needle 10 mls.
- 1% Plain Xylocaine
- Basic dressing pack
- Chlorhexidine solution
- 2 × 5 ml. syringes
- 1 × 23 G. needle
- 1 × 19 G. needle, 1 fenestrated drape
- Surgical mask Sterile gloves
- Trolley
- 22 and 24 size cannula or 2.5 french single lumen catheter
- Arm board with padding Monitoring cable and module
- Disposable pressure monitoring kit # 338
- Hansapor (wound dressing) 15 cm × 8 cm × 1
- Rubbish bin Sterile drape for trolley
- Sterile towel 10 mls
- Normal Saline flush × 2.

B. SETTING UP A TRANSDUCER FOR INVASIVE PRESSURE MANAGEMENT

Procedure

- Attach pressure monitoring kit, to Heparinize Normal Saline bag. Before attachment to bag ensure all luer lock connection are tight on the monitoring kit.
- Place Heparinize Normal Saline bag in pressure bag and inflate to 300 mmHg.
- Prime pressure monitoring kit with Heparinised Normal Saline from infusion bag by pinching butterfly value together. Ensure sample port is also flushed at this time.
- Ensure three way tap is turned off to sample port and red cap is secured in place.
- Maintain sterility of end of pressure monitoring kit by leaving sterile cap at end of line in place.
- Attach monitoring cable to pressure monitoring kit and to bedside monitor. Label as Arterial on bed monitor.
- Zero pressure monitoring kit to atmospheric pressure by pressing zero label on bedside monitor display.

- Lay sterile drape on trolley.
- On sterile field lay out Insite cannula 22-24 G × 1, 2 × 5 ml. syringes, basic dressing pack, 2 /0 black silk on a straight cutting needle, fenestrated drape, 23 G. needle, 1 x 19 G. needle, Hansapor dressing and sterile gloves.
- Under trolley place 10 mls. 1% Plain Xylocaine, Hibitane solution and 10 mls Normal Saline flush × 2.
- While Intensivist is scrubbing lay out sterile towel.
- During procedure assist Intensivist with drawing up solutions and placing appropriate solutions (maintaining sterile field) into dressing pack.
- Once the cannula is in place, remove protector from end of pressure monitoring kit, thread tubing under fenestrated drape and luer lock on to end of Insite cannula. Ensure press line is secured by observing for bleeding at connection site.
- Flush Heparinised Normal Saline through line, same has priming line above.
- Observe bedside monitor for appropriate arterial line wave form tracing.
- After Intensivist has applied dressing, observe site for bleeding. Also check distal and collateral circulation in affected hand.
- Secure affected hand in padded arm board and secure pressure lines to forearm. Arterial Line site should not be compressed by arm board.
- Label dressing with time and date of change.
- Record date and time of next dressing change on flow chart.
- Note in patients' chart above procedure.

C. DRESSING CHANGES TO RADIAL/FEMORAL ARTERIAL LINES

Policy

- Nurses trained to work with pressure lines in an Intensive Care Setting.
- Arterial Catheter dressings must be changed at least every 48hrs or when dressing becomes soiled.
- Area around catheter insertion site will remain free from any signs or symptoms of possible infections.
- Area around catheter insertion site will remain aseptic to decrease changes of possible infection.
- Any sign of infection or possible infection will be reported to the Physician for assessment at the earliest possible moment.

Outcomes

- The area around the catheter insertion site is to remain infection free during the hospital stay of the patient.
- If signs of infection do occur, arrangements must be made with the Physician for earliest possible site changed to be carried out.

Equipment

- Dressing pack × 1 wound dressing 15cm × 8cm × 1cm
- Betadine solution
- Rubbish bin
- Micropore tape
- Overbed table

Procedure

- Explain the procedure to child/parent prior to commencement.
- Aseptic preparation prior to commencing procedure.
- Prepare dressing pack at bedside on overbed table prior to positioning patient.
- Remove armband and place arm on bed with dressing facing up. If patient is restless have second nurse to secure limb to avoid accidental removal of arterial line.
- Remove old dressing and check site for erythema, drainage, tenderness, suture integrity and catheter position.
- Clean area around insertion site with Betadine solution, allow area to dry before applying dressing.
- Ensure pressure line loops over top of dressing.
- Use micropore tape to secure pressure line and transducer so it will not interfere when armboard placement.
- Replace armboard and secure with velcro straps.
- Check monitor to ensure adequate wave form, depressed wave form may indicate a bend in the arterial line.
- Label dressing with time and date of change.
- Record date and time of next dressing change on flow chart.
- Note in patient's chart condition of insertion site and inform Physician of signs of infection.

D. REMOVAL OF ARTERIAL LINE

Policy

- Arterial Lines are to be removed prior to transferring patients to the ward * Arterial Lines sites should be rotated at least every seven (7) days or sooner if infection occurs.
- Post removal Arterial Line site must be observed for bleeding, bruising and swelling frequently over the next 24 hours.
- Upon removal of the arterial Line, Universal precautions must be maintained to avoid contamination of the health care worker through exposure to blood borne pathogens.
- Aseptic technique is used at the insertion site to decrease chances of infection to the patient.

Outcomes

- The area around the catheter insertion site is to remain infection free during the hospital stay of the patient.
- If signs of infection do occur, arrangements must be made with the Physician for earliest possible site changed to be carried out.
- There will be no excessive blood loss, swelling or bruising post removal of Arterial Line

Equipment

- Dressing pack × 1 Elastoplast dressing
- Hibitane solution
- Rubbish bin
- 10cm × 10cm gauze Suture cutter

Procedure

- Explain the procedure to child/parent prior to commencement.
- Aseptic preparation prior to commencing procedure.
- Prepare dressing pack at bedside on over bed table prior to positioning patient.
- Remove armband and place arm on bed with dressing facing up. If patient restless have second nurse to secure limb to avoid accidental removal of Arterial line.
- Ensure pressure bag is clamped off to Arterial Line
- Remove old dressing and check site for erythema, drainage, tenderness, suture integrity and catheter position.
- Clean area around insertion site with Betadine solution.
- Remove sutures holding in Arterial Line. Protect against accidental removal of the Arterial Line at this point to avoid unnecessary blood lose from artery* Place sterile gauze over insertion site and apply pressure to site while withdrawing Arterial Line.
- Pressure should be maintained at least 5 minutes over site to prevent blood loss and excessive bruising and swelling. * Longer periods of applied pressure will be necessary if the patient has been anti-coagulated *Observe the site and when bleeding and swelling have stopped remove old gauze. Applied new sterile gauze over insertion site and secure with Elastoplast dressing.
- Continue to observe site for bleeding.
- Chart that Arterial line has been removed time, date and condition of catheter. Chart condition of patients skin i.e. swelling, redness or discharge.

Alert

- Arterial Lines are a direct access to the patients arterial blood circulation hence if contaminated in any way may lead to severe systemic infection.

9. PROCEDURE: PERICARDIOCENTESIS

1. *Policy:*
   a. This procedure must be performed by consultant intensivist or cardiologist, trainees under supervision.
   b. Confirmation of pericardial effusion or tamponade must be made with echocardiography prior to procedure.
2. *Indications:*
   a. Symptomatic pericardial effusion (tamponade)
   b. Pneumopericardium.
3. *Procedure:*
   a. Strict aseptic technique.
   b. Local anesthetic infiltration if awake patient.
   c. This procedure is greatly facilitated using echocardiography guidance
   d. Technique: Seldinger technique and insertion of a pigtail catheter
      i. Small incision under xiphisternum
      ii. Insert needle on syringe at 45 degrees from the horizontal axis and aim for tip of left shoulder
      iii. Advance slowly and aspirate until confirmation by aspirating blood or serous fluid
      iv. Insert catheter using Seldinger technique over guidewire.
      v. Confirm placement by aspiration and/or echocardiography
      vi. Check CXR (pneumothorax)
      vii. Suture and occlusive dressing if leaving for > 24 hours.
4. *Complications:*
   a. Arrhythmias
   b. Cardiac tamponade
   c. Myocardial laceration
   d. Pneumothorax, pneumopericardium
   e. Liver laceration

10. PROCEDURE THORACOCENTESIS AND CHEST TUBE PLACEMENT (FIG. 10.6)

Primary indications for thoracocentesis are therapeutic; to relieve dyspnea or improve ventilation and gas exchange, or diagnostic; to determine the etiology of pleural effusion. The procedure should be avoided if overlying skin is affected by herpes zoster or if the patient has coagulopathy.

Sizes of chest tubes

Neonates
8, 10, 12 Fr

Pediatrics
14, 16, 20 Fr

Pigtail catheters can also be placed using Seldingers guidewire technique.

Fig. 10.5 shows a massive tension pneumothorax on the right side.

Procedure

Sedation is usually necessary. Intravenous benzodiazepines with or without narcotics are usually sufficient. Ketamine can also be used.

The patient should be positioned with his back vertical. In critically ill patients, decubitus position may be used to keep pleural fluid in most dependent position. Percussion note in such areas would be dull. After local anesthetic infiltration and cleaning the site, the needle is passed at the superior border of the rib to avoid intercostal nerve and vessels.

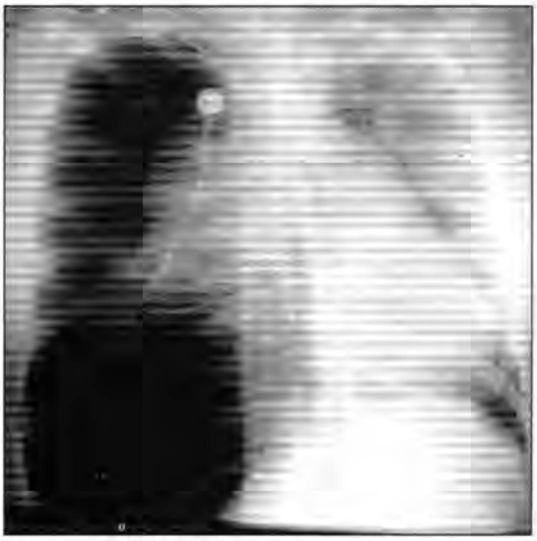

Fig. 10.5: Right pneumothorax

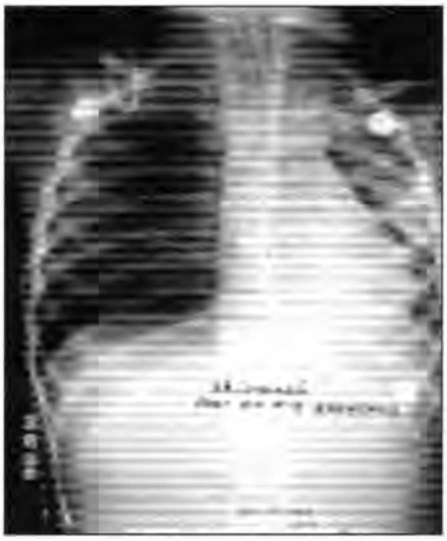

Fig. 10.6: Chest tubes in place

Site of entry is usually at the 5th inter-costal space in mid axillary line or the posterior axillary line.Alternatively for drainage of pneumothorax 2nd intercostal space in midclavicular line can be used.The wound is dissected with the dissecting forceps and a puncture is made once the depth level of parietal pleura is reached.A chest tube is now inserted held with a curved artery forceps , once inserted, it is pushed to at least 5 to 6 centimeters, then sutured in place. Air or fluid should be freely drained. If pneumothorax is the case then a negative pressure of minus 10 centimeters may be applied to the drainage system .

Column of the fluid should move freely with respiratory movements. Exact placement should be checked by obtaining the chest radiograph. Use of trocar to place chest tube is controversial due to associated risk of perforation of lung tissue.

11. CARE OF THE PATIENT WITH CHEST TUBE

Water Seal Drainage

Definition

Water seal drainage is a closed chest drainage system maintained to allow air and fluid to escape from the pleural space with each exhalation and to prevent their return flow with each inhalation. A water seal means water in the bottle seals off atmospheric air, preventing atmospheric air from entering the chest drainage tube and thus from entering pleural space.

Purpose

1. To remove fluid and air from the pleural space after thoracic, thoracoabdominal surgeries, chest injuries involving pleura, spontaneous pneumothorax or pyothorax.
2. To re-establish normal negative pressure in the pleural space.
3. To promote re-expansion of the lungs with opposition and cohesion of the parietal and visceral pleura.
4. To restore the normal pulmonary ventilation.
5. To prevent reflux (return flow) of air and fluid back into the pleural space from the drainage apparatus.
6. To prevent shifting of the mediastinum and collapse of the lung tissue by equalizing pressure on both sides.

Methods of Water Seal Drainage System

1. One bottle method
2. Two bottles method
3. Three bottles method

One Bottle Method

It consists of a bottle with 100ml normal saline closed with a tight rubber stopper with two holes in it. Two hollow tubes (one short and one long) are inserted through the holes in the stopper. One end of the long tube is kept below the fluid level (3-5 cm) in bottle with the other end attached to chest catheter. The other tube acts as air vent .

Two Bottles Method

It consists of an empty drainage bottle placed between the patient and one water seal bottle.

Three Bottles Method

In this method, a suction control bottle is added which is connected to a mechanical suction apparatus, as shown in the figure below: The mechanical suction speeds up the expulsion of the air and fluid from the pleural space.

General Instructions

1. Two rubber clamps are kept at the bedside of the patient to clamp if any emergency arises.

2. Expect in emergency in which clamping is indicated, do not clamp the chest tube without an order to do so. The collection of air in the pleural cavity may cause tension pneumothorax and mediastinal shift.
3. Apparatus for closed chest drainage must be kept at a lower level than the patient's chest. Raising the apparatus to the level of the chest causes back flow of air and fluid into the pleural cavity.
4. When shifting the patient from one place to another, the chest tubes are double clamped and the drainage apparatus may then be placed on the top of the patient's bed during transportation. Never open the clamps on the drainage tubing if the apparatus is above the level of the patient's chest or if the connections are separated.
5. A semi-Fowler's position aids in the drainage from the pleural cavity. Position is adjusted in such a way that the patient is not lying over the tubing and blocking the drainage.
6. Drainage tubing should neither be too long nor too short as it should provide freedom to move in bed and simultaneously, it should not form any loops which may obstruct the drainage of air and fluid from pleural cavity.
7. Check the patency of the drainage tube and chest catheters frequently. To remove kinks and blockage with blood clots in early post-operative period, the drainage tubes are milked every 30 to 60 minutes.
8. Bottles in the drainage apparatus are sealed with tight stoppers and all connections are taped to ensure air-tight drainage system.
9. Observe strict asepsis to prevent introduction of infection into the pleural cavity. Maintain aseptic technique. Wash hands thoroughly whenever the bottles, tubing and connection are changed. Also protect open ends of the tubes with sterile dressings.
10. Encourage patients of closed chest drainage to cough and to take deep breaths which will clear the bronchi of secretions and also promote lung expansion.
11. Chest drainage tubes are always connected to the tubes that are immersed in water to keep it as water seal drainage system.
12. Observe the oscillating movement of the fluid up and down in the water seal tube and intermittent bubbling in water seal and also collection of drainage in bottle. Excessive bubbling or constant bubbling or constant bubbling should be reported.
13. Observe and report immediately about rapid, shallow breathing, cyanosis, symptoms of haemorrhage or subcutaneous emphysema. Patient's status should be assessed by vital signs and appearance frequently and if suction applied, amount of negative pressure should be controlled by a suction control bottle and adjust suction control tube depth under water level.
14. Chest catheters are removed only on physician's order before a chest X-ray is done to make sure that the lungs are fully expanded. After removal, wound should be covered with sterile petrolatum gauze and a firm dressing applied over the wound with wide strips of adhesive tapes. Observe patient for any respiratory distress, during transportation. Never open the clamps on the drainage tubing if the apparatus above the level of the patient's chest or if the connections are separated.
15. Unclamp the chest catheter and make certain its proper functioning. Make sure there is fluctuation of the fluid level in the long glass tube with respiration.
16. Watch vital signs and report if any deterioration occurs.
17. Chart the amount, character, colour and timing of the drainage fluid in intake and output chart and nurse's record
18. Make the patient comfortable
19. Remove the articles except hemostats from the bedside. Wash and keep them, send the water seal apparatus for sterilization
20. Ensure periodically the patency of tube and functioning of water seal apparatus.

12. URINARY CATHETERIZATION

1. Use 6Fr/8Fr catheter
2. Management protocol: In small infant small NG tube can be used.
    a. Aseptic technique at insertion.
        i. Hand disinfection: surgical scrub with chlorhexidine for >1 minute
        ii. Sterile barrier: gloves and sterile drapes.
        iii. Skin prep: chlorhexidine 1%
    b. Local anaesthesia gel in all patients.
    c. Foley catheters for 7 days and change to silastic thereafter if prolonged catheterisation is anticipated. (ie > 14 days)
    d. Remove catheters in anuric patients and perform intermittent catheterisation weekly, or as indicated.

13. SUCTIONING A PATIENT WITH A TRACHEOSTOMY TUBE

Policy

- Management and care of tracheostomy tube through suctioning may be undertaken by Nurses, Physiotherapists and Physician
- In emergency situations all Registered Nurses may perform suctioning procedures on tracheostomies.
- Aseptic technique will be used when suctioning trachea.
- Suction catheters should be less than half the size of the trachea tube insitu.
- During suctioning procedure the catheter should only occluded for 5 second intervals.
- The catheter should be inserted into the trachea tube with gentle pressure and withdrawn from the trachea tube using a rotating technique.
- The patient should be monitored by oximetry for O_2 saturation during the procedure.
- The need for suctioning should be assessed at least every two hours or more frequently as need arises.
- Suctioning should be performed PRN or at frequent intervals as ordered by Physician.
- Over suctioning should be avoided to decrease potential damage to patients airway.

Outcomes

- Explain the procedure to the child/parent prior to procedure.
- Aseptic preparation prior to commencing procedure.
- Open sterile gloves and suction catheter packages.
- Place clean Latex glove on non-dominant hand. Place on eye protection at this time.
- Clean end of blue bodai connector on trachea tube with alcohol swab.
- Place patient on Oxygen monitor if available or patient in unstable respiratory condition for monitoring of oxygen saturation's during procedure.
- Pre-oxygenate patient with ambu bag on a 100% O_2 for 2 minutes prior to suctioning.
- Turn on suctioning equipment with suction tubing and place near head of patient.
- Place sterile glove on dominant hand and connect suction catheter to suction tubing.
- From this stage the suction catheter should only be handled using the sterile glove.
- Using aseptic technique, pass the suction catheter through blue bodai connector down into trachea tube entering the patients upper airway. The suction catheter is advanced in this way until the patient coughs. Do not apply suction up to this point.
- Apply suctioning withdraw suction catheter with a rotating motion and apply suctioning only at 5 second intervals.
- If repeated suctioning is to be performed allow the patient rest for several minutes to regain adequate oxygen levels. Patient may be ventilated with Lardel bag on a 100% O_2 to being O2 back up to an acceptable range or if patient becomes distressed during procedure.
- Clean out patient oral pharyngeal airway with either suction catheter or yankeur sucker. Suction catheter must never be placed back in trachea tube after being placed in either patients mouth or nasal passage ways.
- At end of procedure discard suction catheter in trash bin. Rinse suction tubing with water.

Post Procedure

- Monitor patients respiratory effort and oxygen saturation.
- Note amount, colour and consistency of tracheal aspiration in nurses notes and ICU flow sheet.
- Also chart how patient tolerated procedure and any problems encountered.

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14. SUCTIONING A PATIENT WITH AN ENDOTRACHEAL TUBE

Standards

- Aseptic technique will be used when suctioning.
- Suction catheters should be less than half the size of the endotracheal tube insitu.
- During suctioning procedure the catheter should only occluded for 5 second intervals.
- The catheter should be inserted into the trachea tube with gentle pressure and withdrawn from the trachea tube using a rotating technique.
- The patient should be monitored by oximetry for O_2 saturation during the procedure.
- The need for suctioning should be assessed at least every two hours or more frequently as need arises.
- Suctioning should be performed PRN or at frequent intervals as ordered by Physician.
- Over suctioning should be avoided to decrease potential damage to patient's airway and hypoxic episodes.
  In patients with ARDS on high PEEP, closed suction system is preferable, however if unavailable, then hand bagging with administration of PEEP should be learned to prevent derecruitment(collapse) during suctioning.

Outcomes

- Explain the procedure to the patient/child prior to procedure.
- Aseptic preparation prior to commencing procedure.
- Open sterile gloves and suction catheter packages.
- Place clean Latex glove on non-dominate hand. Place on eye protection at this time.
- Clean end of blue bodai connector on trachea tube with alcohol swab.
- Place patient on Oxygen monitor if available or patient in unstable respiratory condition for monitoring of oxygen saturation's during procedure.
- Pre-oxygenate patient with ambu bag on a 100% O_2 for 2 minutes prior to suctioning. - Turn on suctioning equipment with suction tubing and place near head of patient.
- Place sterile glove on dominate hand and connect suction catheter to suction tubing.
- From this stage the suction catheter should only be handled using the sterile glove.
- Using aseptic technique, pass the suction catheter through blue bodai connector down into trachea tube entering the patients upper airway. The suction catheter is advanced in this way until the patient coughs. Do not apply suction up to this point.
- Apply suctioning withdraw suction catheter with a rotating motion and apply suctioning only at 5 second intervals.
- If repeated suctioning is to be performed allow the patient rest for several minutes to regain adequate oxygen levels. Patient may be ventilated with Lardel bag on a 100% O_2 to being O_2 back up to an acceptable range or if patient becomes distressed during procedure.
- Clean out patient oral pharyngeal airway with either suction catheter or yankeur sucker. Suction catheter must never be placed back in trachea tube after being placed in either patients mouth or nasal passage ways.
- At end of procedure discard suction catheter in trash bin. Rinse suction tubing with water.

Post Procedure

- Monitor patient's respiratory effort and oxygen saturation.
- Note amount, colour and consistency of tracheal aspiration in nurses notes and ICU flow sheet. Also chart how patient tolerated procedure and any problems encountered.

15. TRACHEOSTOMY CARE

Definition

A tracheostomy is an external opening made into the trachea.

Purpose

1. To keep the tube free from mucous/ to maintain patency of the tube
2. To prevent the tube being pulled out or coughed out.
3. To watch the tracheostomy wound, and prevent infection.
4. To provide moist air for patient to breathe.

General Instructions

1. While inserting the catheter keep Y vent open to prevent tissue injury.
2. Use rotatory movements while withdrawing the catheter.
3. Do not suction the patient more than 15 seconds at a time and rest at least 3 minutes between suctioning.
4. For thick secretions, instill sterile saline solution about 0.5 ml. to 2 ml. by a sterile syringe. Remove the needle before instilling. If the tape is being changed, always keep tracheal dilators near by so that if tube comes out, tracheal dilators can be used to prevent tracheal spasm.
5. Aseptic technique should be maintained.

Articles Required

1. A tray containing :
    - Sterile saline bottle
    - Sterile catheters (disposable or red rubber catheter)
    - Size- 14 fr for adults , 8 to 10 fr for children
    - Sterile gloves
    - Sterile bowls – 2 Nos
    - Glass Y connection
    - Sterile syringe
    - Suction machine
    - Sterile face mask and hand towel
    - Mackintosh and towel
    - Dressing set (containing artery forceps and thumb forceps)
    - Surgical drum containing sterile gauze pieces
    - Antiseptic solution (Betadine)
    - Paraffin gauze
    - Tape for tying
    - Kidney tray and paper bag
    - Swab stick
    - A bowl with plain cold water
    - A bowl with warm water
2. Screen for privacy

Procedure

1. Explain the procedure to the patient
2. Screen the patient
3. Bring the articles to the bedside and arrange them
4. Put on the mask. Wash hands and dry them
5. Protect the patient's garments with mackintosh and towel
6. Put on gloves, remove the inner tube from the T-tube and place it in a bowl containing water
7. Switch on the suction machine with left hand and keeping right hand uncontaminated
8. Pour sterile saline in sterile bowl with left hand
9. Pick up the sterile catheter right hand and attach it to the Y-connection held by left hand
10. Rinse the lumen of the catheter with saline in bowl
11. Gently insert the catheter into the tracheostomy tube 4-6 inches. Do not apply suction while inserting the catheter. It is done by keeping the Y vent open (If the glass connection is plain then pinch the catheter in order to avoid suction)
12. Apply suction by closing the Y vent (In case of plain glass connection, release the pinch). Then slowly withdraw the catheter while rotating it. Don't apply suction for more than 15 seconds to prevent hypoxia.
13. Now pick up a sterile gauze piece form the bowl and wipe off the catheter from top to the tip of the catheter, once. Discard the gauze in paper bag. Rinse the catheter again in sterile saline by right hand.
14. Repeat the suction procedure until copious secretions are removed or patient is comfortable.
15. Then discard the catheter if it is disposable. If it is red rubber catheter keep it in the kidney tray.
16. Dressing

    With left hand, remove the dressing
    Open the dressing set and pour saline in bowl
    First clean the wound then clean the rim of the tracheostomy tube
    Discard the used saline in the kidney tray
    Take Betadine solution in the bowl and dilute it with saline. Dip folded paraffin gauze in Betadine solution and squeeze it with the forceps
    Place it under the tube and over the wound
    Take one moist gauze piece and place over the tube
    Replace the articles / screen
    Make the patient comfortable
17. Record the time of suctioning, type of secretions whether loose or thick, tenacious, colour of mucous, smell (if foul smelling it indicates infection), type of dressing applied, condition of the patient.
18. Clean the inner tube under cold running water to remove the mucous adhering to it. Keep it dipped in sodium bicarbonate 1:1 solution in water to soften the secretions. Clean the tube with swab stick. Then rinse it thoroughly under running water, sterilize it in boiling water for 5 minutes.

19. Re-insert the inner cannula only after suctioning the outer cannula to remove the secretions. Lock the inner cannula securely to the outer tube.

16. TRACHEOSTOMY DRESSING

Policy

- The tracheal tube will be secured in the midline position.
- Aseptic technique to be used when changing tracheostomy dressing.
- Dressing to be changed for the first time 24hrs post procedure.
- Dressing to be changed thereafter once a shift or PRN when soiled.
- Tie tapes holding tracheostomy tube will not be secured so tight around neck as to occlude patients circulation.

Outcomes

- Complication of tracheal stenosis and erosion are minimised by securing the tracheal tube in midline position.
- The patient tracheostomy site will remain infection free during his or her stay in hospital.

Equipment

- Basic dressing pack
- Normal saline
- 2 pack sterile gauze 10x10cm
- 2 × _ in white cotton tape x 1m length

Procedure

- Explain the procedure to the patient prior to procedure.
- Aseptic preparation prior to commencing procedure.
- Prepare dressing pack at bedside prior to positioning patient.
- Suction patient (refer to Suctioning of patient with tracheostomy tube).
- Arrange for second nurse to hold the tracheostomy tube.
- Remove old dressing and ties.
- Swab around tracheal stoma with normal saline until the area is cleaned.
- Fold sterile gauze squares in half and place on under each flange of the tracheostomy tube.
- Attach cotton tape to tracheostomy tube flange by passing doubled cotton tape up through opening in flange then threading loose ends up through loop. The end result should have two tails extending out from flange, one tail being 15cm of the one metre length. Repeat procedure for the side of the flange.
- Thread the two long portions of the cotton tape behind the patients head.
- The long cotton tape are then to be tied to the shorter tied leaving at least a two finger space between patient and tie tapes.
- Ensure patients comfort with new dressing.
- Test cuff press with cuffed tracheostomy tubes. Pressure should be <25cm H_2O

17. INSERTION OF PERITONEAL DIALYSIS CATHETER

Purpose

A. *Indication in the immediate postoperative period.*
   1 Anuria resistant to frusemide 5 mg/kg.
   2 Oliguria (<0.5 ml/kg/h) unresponsive to diuretics in unstable patients e.g. Children with established low cardiac output, capillary leak, or fluid overload.
   3 Borderline normal urine output unresponsive to diuretics in severely fluid overload patients.
   4 Hyperkalemia (k+ > 6 mmol/l).

B. *Indications during prolonged intensive care.*
   1 Volume overload refractory to diuretics.
   2 Hyperkalemia.
   3 Metabolic acidosis of non-cardiac origin (pH < 7.2).
   4 Urea >30 mmol/l or rising rapidly.
   5 Neurological symptoms secondary to uremia or electrolyte abnormality.

Articles Required

1. P.D. Catheter.(Tenkhoff)
2. B.T. Set,
3. Sterile gloves,
4. Surgical blade,
5. Dressing set,
6. Pedia drip set,
7. P.D. Flush,
8. Urinary drainage bag,
9. Dynaplast,
10. Sterile gauze pieces,
11. Tegaderm,
12. Silk Thread,
13. Three ways,
14. 5cc Syringe.

Procedure

1. Place the baby in supine position on bed.
2. Ensure that the bladder is empty.
3. Select P.D. Catheter insertion site: usually midline 1-3 cm below umbilicus, or right or left lateral sites, lateral to borders of rectus. Avoid enlarged organs and surgically scarred areas.
4. Provide appropriate sedation/analgesia. The skin will be infiltrated with 1% lignocaine.
5. Standard aseptic technique (mask, gown, gloves). Clean skin with alcoholic povidone, iodine, allowing time to dry.
6. Two types of P.D. catheter are available in PICU – rigid (black) cook catheters and percutaneous tenchkoff catheters. The basic insertion technique is similar for both types of catheter.

7. Select a P.D.Catheter. In addition, select an Abbocath cannula of a size which will allow the catheter guide wire to introduce through it.
8. Introduce the Abbocath into the peritoneum. A pop is usually perceived as the device breaches the peritoneum.
9. The Abbocath is advanced fully into the peritoneal cavity in the direction of the pelvis.
10. Following withdrawal of the needle free reflux of peritoneal fluid may be noticed, and saline can be injected freely through the cannula. At this point the guide wire is introduced through the cannula.
11. The cannula is withdrawn over the guide wire and the dilator,+ - sheath and catheter are placed sequentially.
12. Details vary slightly between cook and tenchkoff catheters.
13. Tenchkoff catheters can be tunneled, although this is not essential for acute dialysis.
14. A purse string suture round the catheter insertion site helps to seal the peritoneum.
15. A new PD catheter should be cycled with heparanised PD fluid (200 units heparin per litre). Heparin may be omitted once the effluent is clear and not blood stained.
16. Secure the catheter with adhesive dressings with split gauze swabs round the catheter.
17. Obtain an abdo X-ray to confirm catheter position.

Care of PD Catheters

As one of the most common and serious complications of PD catheterization is the development of peritonitis. Minimise infective complications by:

1. Treating PD system aseptically,
2. Regular inspection of skin entry site of infection,
3. Daily culture of PD effluent.

General Instructions

Usually manifested by problems with outflow.

Cause	Remedy
Catheter Kinking,	Slight repositioning,
Occlusion of catheter by fibrin plugs,	Heparin flushing consider Streptokinase(STK+),
Occlusion of catheter by omentum	Attempt repositioning by slight withdrawal,
Catheter malposition.	Replace at new site.

Streptokinase regime: Dilute STK+ to 10,000 units/ml. Flush to fill catheter and soak catheter tip. Clamp for 2 hours. Repeat *1 if unsuccessful.

Basic Peritoneal Dialysis Regime

Dialysis is usually started with isotonic dialysis e.g. using No.61Diaflex solution, which is a balanced salt solution with a sodium content of 140 mmol/l and 1.36% glucose. Allow sodium base solution (Na 130) may be used in patients with hypernatremia which is not due fluid loss i.e. they are euvolaemic.

Additives;

Heparin 200 units/l

K+ 0-4 mmol/l depending on serum potassium.

50% glucose (Added to increase tonicity of fluid, and facilitate fluid removal).

10ml 50% glucose per litre increase the glucose concentration by 0.5%. Glucose concentrations up to 3.86% can be used during PD to increase fluid removal. This is especially indicated in fluid overloaded patients, or in those in whom space must be created for parentral or enteral nutrition. No patient with fully functioning peritoneal dialysis should ever be denied adequate caloric intake because of fluid input restriction.

Bi-carbonate dialysis:- Dialysis is occasionally indicated in patients who are severely acidotic. As the required bicarbonate mixtures are not stable, solutions must be freshly prepared as follows;

BAG 1 500mls 5% glucose

Step	1	Remove	40ml from the bag
	2	Add	40ml 8.4% sodium bi carbonate
	3	Add	5ml 30% sodium bicarbonate
	4	Add	200u Heparin

BAG 2

Mix in 1:1 ratio in burette

Note

1. This gives a final concentration of Na 140 mmol/l, HCO_3 40 mmol/l, glucose 2.5%.
2. The solution does not contain any calcium. Follow ionized calciums carefully and give oral or i/v supplements as indicated by measurements.

PD Cycles

Usually 20-30 ml/kg/cycle with hourly cycles.

10ml/kg/cycles (minidialysis) every 30-60 minutes in haemodynamically compromised patients.(often 10 min.in 20 mind dwell and drain).

Comments

1. Peritoneal dialysis takes time to establish.Therefore problems should be anticipated, and moves to establish dialysis taken early.
2. Hyperglycaemia can occur in patients on PD as glucose may be absorbed from dialysate. Management may be either reducing the glucose concentration in PD fluid, reducing nutritional glucose intake, or starting in I/V insulin infusion. Caloric intake must remain optimal.

CHAPTER

Procedures in Pediatric Intensive Care Unit

Praveen Khilnan

This chapter is intended to familiarize the reader with the following procedures commonly used in the pediatric intensive care unit. Airway mangement and endotracheal intubation are discussed in a separate chapter.

1. Peripheral venous and intraosseous access
2. Arterial catheterization
3. Umbilical arterial and venous catheterization
4. Vascular cutdown
5. Central venous catheterization and PICC line
6. Lumbar puncture
7. Thoracentesis and chest tube placement
8. Pericardiocentesis
9. Abdominal paracentesis.
10. Transurethral catheterization and intrabdominal pressure measurement

Peripheral Venous and Intraosseous Access

Basilic, cephalic and median cubital veins are commonly used. Interdigital veins of the hand, scalp veins and the saphenous veins at the ankle are also reliable sites. External jugular vein is an excellent cannulation site that is under utilized. Dilated abdominal veins may also be used as a last resort especially in premature infants. Visualization or palpation of peripheral veins may be enhanced with tourniquet application, dependent positioning, heat or transillumination. An important practical hint to be kept in mind is that once the catheter on a needle has entered the vein and blood return is seen, only the tip of the needle may lie in the vein since the needle tip projects beyond the catheter tip. Removal of the needle at this time may result in a failed attempt at threading the catheter further in the vein It is advisable, therefore, to push the catheter on needle a little further in the vein to ensure entry o both the catheter and the needle.

Complications of peripheral intravenous catheterization include local infection, bacteremia, phlebitis infiltration with or without skin necrosis, thrombosi and embolism.

Intraosseous Access

Intraosseous infusion remains largely a lifesavin resuscitative measure for short term. It is used i patients less than 6 years of age. Preferred site i the flat anteromedial surface of the proximal tibia 1 cm inferior to and 1 cm medial to the tibial tubercle Other sites are the midline of the distal femur, 3 c proximal to the lateral condyle, the distal tibia jus proximal to the medial malleolus (Fig. 11.1).

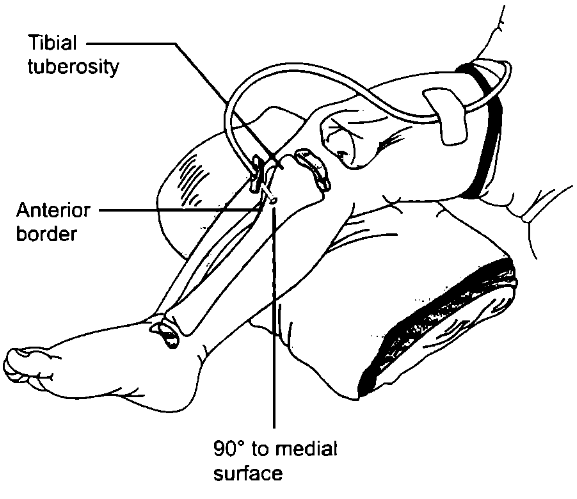


Fig. 11.1: Technique of intraosseous access

After the skin site preparation and local anesthesia, a 13 or 18 gauge bone marrow needle with stylet is used with a rotating or screwing motion in the bone. The needle should be pointing away from the joint until a give is felt indicating marrow entry. Bone marrow is aspirated, needle connected to intravenous tubing. Pressure required to push fluid should not be different than that required with a regular intravenous line. There should be no skin infiltration if the intraosseous needle is in place. The other side of the leg should be looked at for needle tip if too deep penetration has occurred. Almost all fluids and medications can be given via the intraosseous route.

Complications include fracture, osteomyelitis, extravasation of fluid in subcutaneous tissue. Any known bony disease (e.g., osteogenesis imperfecta or bone tumor) should be treated as a contraindication to the procedure. Fractured limb should not be used for intraosseous needle placement.

Arterial Catheterization

Arterial catheterization is done for patients requiring continuous intra-arterial blood pressure monitoring or frequent arterial blood gas determinations. Any of the following arteries may be used: radial, posterior tibial, dorsalis pedis, femoral or axillary artery. In a neonate, the umbilical artery is most commonly used. Radial arterial cannulation in neonates has recently gained some popu-larity due to relatively lower complication rate compared to umbilical arterial catheters.

Radial Arterial Catheterization (Fig. 11.2)

A 22 gauge or 24 catheter over the needle can be used. A 15 or 18 gauge (SWG) guide wire should be available.

Allen's test: Allen's test for collateral circulation must be performed. After occluding both radial and ulnar arteries for 30 seconds, ulnar arterial site is released. In less than 3-4 seconds, the palm shows signs of circulation by the return of pink color. If the palm remains pale, ulnar collateral circulation is insufficient; radial arterial cannulation should not be performed.

After cleaning the site and administration of local anesthetic, the catheter on the needle (angiocath) is inserted at a 30 degree angle at the site of maximal radial arterial pulsation with wrist extended. Catheter is advanced with the needle until blood return is obtained. The needle is removed and the catheter is advanced into the artery. Sometimes it is difficult to advance the catheter, even though there is blood spruting at the end of the catheter. This may be explained by the spasm of the muscular layer of the artery around the catheter. The catheter should not be pushed any further, a 15 or 18 gauge guide wire may be passed via the catheter. If the guide wire passes freely, the catheter can usually be easily passed over the guide wire into the artery. If one site has been tried and the procedure is unsuccessful, the pulse in that site may become weak due to arterial spasm. Another site should be tried. After 10-15 minutes, the pulse may return at the previous cannulation site and recannulation can be tried again. If after multiple attempts at the procedure is unsuccessful, surgical arterial cutdown is recommended. The technique is similar to venous cutdown described later in this chapter. In desperate situations, ulnar arterial catheterization may be performed provided radial collateral circulation has been tested. Brachial arterial cannulation is not usually recommended due to poor distal collateral circulation.

Recently, axillary arterial line placement in pediatrics has been reported to be safe and effective. Axillary arterial pulsation can be felt in the axilla

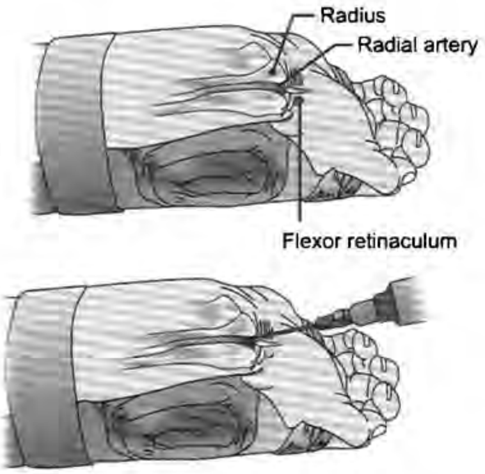


Fig. 11.2: Radial arterial anatomy and cannulation

just beneath the anterior axillary fold formed by the pectoralis major muscle. The artery is cannulated with arm abducted at right angle to the shoulder. Cannulation may be assisted with the guide wire technique as described for radial artery.

Normal saline with 1 unit heparin/cc at a rate of 2 cc/hour can usually be used as a continuous flush via transducer tubing to ensure the patency of the arterial line. Arterial line should be handled with antiseptic precautions to prevent infection.

Complications of arterial cannulation mainly include distal ischemia and necrosis. Capillary circulation, pulses and temperature in area distal to the arterial line placement should be monitored closely as well as the observation of skin site for blanching or ischemia where the arterial line is placed. If any signs of ischemia are noticed, the radial arterial catheter should be removed to prevent skin ulcer formation.

Femoral Arterial Catheterization (Fig.11.3)

Femoral arterial catheterization should be tried after all attempts at peripheral arterial catheterization have failed. Needle with a syringe is used to enter 2 cm below the level of inguinal ligament at the point of maximum pulsation in the inguinal region.

Femoral vein lies medial to the femoral artery. The blood return from the artery is pulsatile and bright red compared to the femoral vein. As soon as the blood return is obtained, an appropriate size guide wire is passed via the needle. The catheter may then be passed over the guide wire. A 3 French 4 cm long catheter is usually used. In younger children and neonates, a 22 gauge angiocath (catheter over the needle) can be used. Femoral lines must be sutured in place due to risk of dislodgement with patient movement or dressing change. Injury to the hip joint is rare, but an important complication of femoral arterial line placement in neonates. Other complications include femoral arterial thrombosis and distal ischemia of the lower extremity.

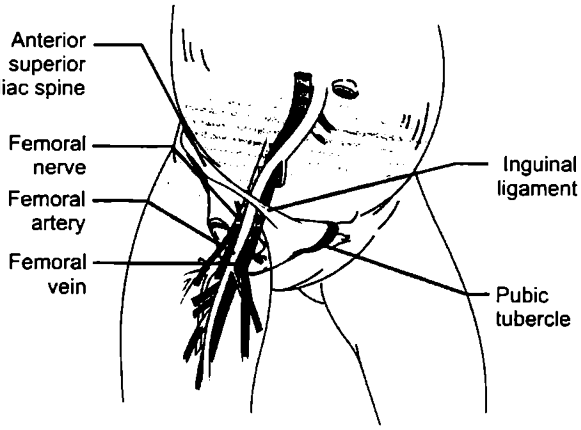


Fig. 11.3: Anatomical landmarks for femoral arterial and venous catheterization

Posterior Tibial and Dorsalis Pedis Arterial Catheterization

Posterior tibial arterial pulsation is felt posterior to medial malleolus. The needle is inserted just posterior to the medial malleolus and parallel to the long axis of the leg. Dorsalis pedis arterial pulsation is maximum at the upper part of the foot, midway between the medial and lateral malleolus anteriorly. The technique of arterial cannulation is essentially similar to radial arterial cannulation.

Umbilical Arterial and Venous Catheterization

Indications for umbilical arterial catheterization in neonates are essentially the same as indications for arterial line placement in infants and children. This procedure is frequently used in neonates up to 7-8 days of age. A 3.5 French umbilical arterial catheter may be used. The umbilical stump is first tied with an umbilical tie (a cotton strip). The skin site and the base of the umbilical cord stump are then cleaned with betadine (or other available skin antiseptic solution). A clean transverse cut of the umbilical stump is made 2.5 cm from the skin with a scalpel blade. It shows two arteries and one vein (vein is larger). A dilator may be used to dilate the artery first. The catheter, itself, can also be used to dilate the artery. Care should be taken not to push the catheter if it does not pass freely, as the catheter could dissect in between the intimal and the muscular layer of the artery, or in between the outer wall of the artery and gelatinous tissue of the umbilical cord. In both cases blood return will not be obtained. The umbilical arterial catheter first goes down then takes an upward course to join the common iliac artery to enter the aorta. This course can be seen on anteroposterior and lateral views of abdominal X-ray films.

The catheter tip should be kept at the level of T3-4 (Thoracic) (high catheter) or below L2 (Lumbar) (low catheter). The rationale being to keep the catheter tip away from the level of origin of the renal arteries to prevent renal artery thrombosis. An X-ray film should always be done to check placement. Rarely, the catheter may advance into the gluteal artery via the internal iliac artery. (This has resulted in ischemic necrosis in the gluteal region.) After the catheter has been inserted, the umbilical cord tie may be released and the catheter sutured in place. The catheter can then be properly secured with tape. Perfusion and color of both legs should be monitored while the umbilical catheter is in place.

Complications of umbilical arterial catheterization include: ischemic necrosis of the leg, gluteal region, or the kidney. Renal arterial thrombosis may result in later renal hypertension. There is no direct correlation between necrotizing enterocolitis and umbilical arterial catheterization although in some cases umbilical arterial catheters have been incriminated. It is, however, conceivable that mesenteric arterial thrombosis induced by an umbilical arterial catheter may induce gut ischemia predisposing to necrotizing enterocolitis in neonates.

Umbilical Venous Catheterization

A 5 French umbilical venous catheter can usually be inserted since the umbilical vein has a larger diameter. The catheter insertion technique is similar to umbilical arterial catheterization, except that the catheter takes an upward course, crosses the ductus venosus to run into the inferior vena cava. The catheter tip should be kept in the lower right atrium. During insertion, the tip of the catheter may turn into one of the hepatic veins; in which case, the catheter should be withdrawn.

Double lumen catheters are now being used to achieve easy access, as well as CVP monitoring and multiple pressor drug infusion in critically ill neonates.

Complications of umbilical venous catheterization include-portal venous thrombosis, hepatic necrosis, infection, thrombosis of the inferior vena cava.

Vascular Cutdown

Vascular cutdown is indicated if all attempts at vascular cannulation have failed. Saphenous venous cutdown is most commonly used. After sterile preparation and local anesthesia, an incision perpendicular to the vein is made 1 cm superior and 1 cm anterior to the medial malleolus. The vein is isolated by spreading the adjacent tissues with a curved hemostat. A silk suture is passed under the vein. The vein can be directly entered with an angiocatheter or Seldinger technique (described below) may be used to introduce the catheter over a guide wire. The wound is closed and dressed. Arterial cutdown may be done using the same technique.

Central Venous Catheterization

Main indication for placing central line in acute setting is for a patient in shock requiring continuous central venous pressure monitoring, fluid boluses and multiple drug infusions. In chronic setting, central lines are mainly used for chemotherapy and total parenteral nutrition. Seldinger technique 14 (described below) has been universally adopted to assist in central line placement.

Seldinger technique: Needle with a syringe is first used to enter the vein. When blood return is obtained, the appropriate size guide wire is passed via the needle and the needle is removed. A dilator (stiff catheter) is now passed after the skin at the guide wire entry site has been nicked with a scalpel tip to allow the entry of the dilator. Dilator is passed firmly along the guide wire to create the path in the subcutaneous tissue, and dilate the entry site to allow the entry of the catheter. Dilator is now removed while the guide wire is in place. The catheter is now passed over the guide wire. The guide wire may now be removed. The catheter is sutured in place.

Double and triple lumen catheters are frequently needed in critically ill children to administer different non-compatible medications and fluids. A guideline for catheter sizes for different age groups is given in Table 11.1. Sites for central venous catheterization include: subclavian, internal jugular and femoral.

Table 11.1: Guidelines for use of peripheral and central venous catheters

Age (years)	*Weight (kg)*	*Central venous catheter (angiocath)*		*Length of the Catheter (cm)*
		(gauge)	*(french size)*	
< 1 year	< 10	22, 24	3.0-3.7	8, 12
1-12 years	10-40	12, 20	4.0	8, 12
> 12 years	> 40	14, 16, 18	5.5, 6.5, 7.0	12, 20

Subclavian Vein Catheterization

Infraclavicular Approach (Fig. 11.4)

Ideal position is 30 degree Trendelenburg position with the roll between the scapulae and arm abducted by the side. Intravenous sedation may be achieved with morphine or ketamine. Local anesthetic (lidocaine) infiltration should still be used. Puncture site is the infraclavicular fossa (depression beneath the midpoint of clavicle medial to shoulder).

A syringe with the needle is held perpendicular to the long axis of the sternum, and parallel to the clavicle. Needle is passed horizontally under the clavicle, and advanced toward, the sternum until blood return is obtained. Guide wire is then passed, the passage must be smooth, transient dysarrhythmias may be observed when the guide wire reaches right atrium. Dilator may now be passed with a screwing motion, and the catheter inserted by Seldinger's technique as described above. Sometimes catheter may turn upwards into internal jugular vein requiring removal of the catheter. Tip of the catheter should be kept at superior vena cava right atrial junction confirmed by X-ray film. A free blood return must be obtained at all times.

Complications (Table 11.2)

Air embolism and pneumothorax are immediate potential complications. Any respiratory distress during subclavian catheter insertion must be taken seriously and X-ray film of the chest should be obtained to rule out pneumothorax. Subclavian arterial puncture is possible and one must stop the procedure wait for five to ten minutes with pressure on the puncture site, then restart the procedure if patient is hemodynamically stable and has no respiratory distress.

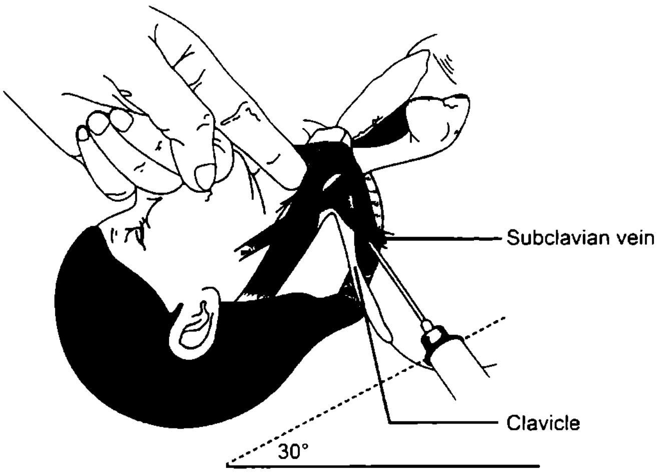


Fig. 11.4: Technique of subclavian venous catheterization: Infraclavicular approach

Late complications include: thrombosis, infection, dysrhythmia, catheter migration, catheter breakage, embolism and pericardial tamponade.

Some authors recommend right subclavian vein catheterization over left subclavian to minimize chances of thoracic duct injury. In author's experience, this has not been a clinically significant issue. Other approaches include supraclavicular and axillary approach. In author's experience, infraclavicular approach is most successful and easy to learn in pediatrics.

Table 11.2: Complication of central venous catheterization

- Pneumothorax
- Bleeding
- Infection
- Arterial puncture
- Venous thrombosis
- Pulmonary embolism
- Dysrhythmias
- Air embolism
- Thoracic duct injury
- Catheter malposition
- Hemothorax
- Nerve injury-Phrenic
- Brachial plexus
- Pericardial effusion/Pericardial tamponade

Internal Jugular Vein Catheterization

Different approaches may be used. The right internal jugular vein is preferred because of the presence of the thoracic duct on the left, and the straight route from right internal jugular vein to right atrium as well as lower pleural dome on the right. Three approaches central, anterior or posterior, may be used in relation to sterno-cleido-mastoid muscle. Patients head is turned to opposite side, and 30 degrees lower with extension at the neck by keeping towel beneath the shoulder on the same side.

Central Approach (Fig. 11.5)

Needle entry is at the apex of triangle formed by sternal and clavicular heads of sternocleidomastoid muscle. The needle is pointed laterally towards ipsilateral nipple 45 degrees posteriorly, until blood return is seen. Needle is not pushed more than 2 centimeters.

Anterior Approach

The needle is inserted halfway along the anterior border of the sterocleidomastoid muscle aiming at the ipsilateral nipple 45 degrees posteriorly as the carotid artery is displaced medially.

Posterior Approach (Fig. 11.6)

The needle is passed behind the posterior border of sternocleidomastoid muscle one third of the muscle's length from its clavicular insertion aiming for the suprasternal notch.

After blood return is obtained, Seldinger technique is used to place the catheter.

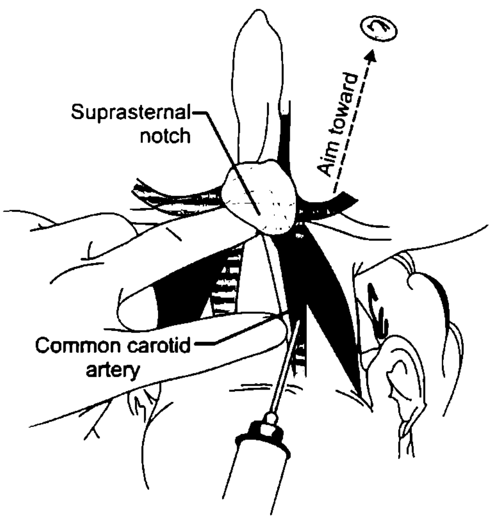


Fig. 11.6: Technique of internal jugular venous catheterization: Posterior approach

Femoral Venous Catheterization

Femoral Vein is Medial to the Artery

After proper sedation, local anesthesia and cleaning the site, the needle is introduced medial to the femoral arterial pulsation at 30 degree angle, 2 cn below the inguinal ligament, until blood return i obtained. Guide wire is then passed through th needle. If the guide wire doesn't pass easily, a super ficial vein may have been punctured. In which case the guide wire takes a tortuous course and get stuck. Guide wire should then be withdrawn an another attempt should be made to puncture th femoral vein. Portable ultrasound guided centra venous access in technology is available to locat the vein in difficult situations, e.g. obese childre due to cost related issues.

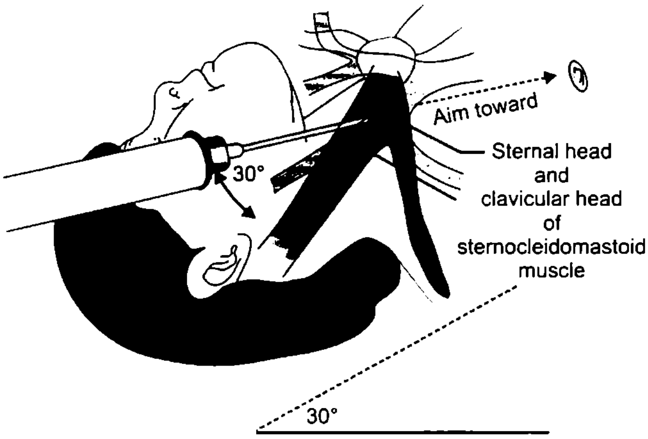

Aim toward
30°
Sternal head and clavicular head of sternocleidomastoid muscle
30°

Fig. 11.5: Technique of internal jugular venous catheterization: Central approach

Percutaneously Inserted Central Catheters (PICC Lines)

Long peripherally inserted radiopaque lines ar available for prolonged antibiotic therapy, chemo therapy, total parenteral nutrition. A typical suc line has a small wire stillette that can be remove after placement. Length of these lines can b shortened to place the tip near the junction o superior vena cava and the right atrium. Smal percutaneous silastic catheters have also been use in neonates for long-term hyperalimentation. Th catheter can be introduced via a breakable butterfl needle used to enter the vein (Per Q cath, Gesco TX). Femoral, subclavian, external jugular or eve scalp vein or median basilic veins may be used. Th catheter tip may be advanced to superior or inferior vena cava as the case may be. Complications associated with these catheters have been reported (e.g. pericardial tamponade, catheter breakage and infection). These lines, eventhough peripherally inserted have to be treated with aseptic precautions same as central lines. Maintenance of these central lines, requires use of 10 unit/cc heparin 1 to 2 ml every eight hours, and additional heparinized (10 u/cc) saline flush after every use.

Lumbar Puncture

Most common indication of lumbar puncture in pediatric intensive care unit is essentially diagnostic, i.e. to rule out bacterial or viral meningitis. Lumbar puncture may also be performed for therapeutic purposes, i.e. progressing neonatal hydrocephalus secondary to intraventricular hemorrhages and for intrathecal drug administration. Right or left lateral position may be used with flexion at the neck and hips to widen the space between the tips of the vertebral spines.

L3-4 or L4-5 interspace is usually used. A 22 gauge spinal needle is passed direct towards umbilicus between tips of the spines of L3-4 or L4-5. After the cleaning of the site and local anesthetic infiltration, skin, subcutaneous tissue and interspinous ligament are first punctured, the needle is then gradually advanced until a give is felt. This indicates ligamentum flavum, dural and arachnoid puncture. The tip of the needle is now in the subarachnoid space. Inner needle may now be removed and cerebrospinal fluid will usually be obtained. If no fluid is obtained, dura may not have been punctured, the needle should be pushed further after replacing the inner needle. The cerebrospinal fluid (CSF) will usually be obtained. If no fluid is obtained and the needle seems to be hitting the bone, the patient's back should be flexed further to widen the intervertebral and interlaminar space. This may allow the needle entry into the subarachnoid space. If blood is obtained, it should be allowed to drip until clear fluid is obtained. The blood will usually clear if the tip of the needle is in the subarachnoid space. If the blood doesn't clear up, the needle should be removed and another interspace should be tried with a new needle. After the CSF has been obtained, the spinal needle may be removed and the puncture wound dressed with sterile gauze. If the patient has focal neurological signs or unilateral dilated pupils, fundus examination to rule out papilledema or a computerized tomographic scan of the head should be obtained to rule out intracranial mass lesion leading to increased intracranial pressure before performing a lumbar puncture. Lumbar puncture, if performed in a patient with increased intracranial pressure, may result in transtentorial or tonsillar herniation due to sudden removal of fluid from spinal canal creating a negative pressure. After the procedure, the patient should lie supine for a few hours to prevent low pressure headache which may result from spinal fluid leak from dural puncture wound. If, however, headache does occur, intravenous fluids can usually be given to increase production of CSF, thereby minimizing the low CSF, pressure headache, in addition to analgesics.

Other complications of this procedure include: introduction of infection (meningitis), hematoma in the subdural or epidural space and rarely nerve root injury resulting in neurological symptoms in the lower extremity. Backache, if occurs, is usually temporary.

Thoracentesis and Chest Tube Placement

Primary indications for thoracentesis are therapeutic; to relieve dyspnea or improve ventilation and gas exchange, or diagnostic; to determine the etiology of pleural effusion. The procedure should be avoided if overlying skin is affected by herpes zoster or if the patient has coagulopathy.

Sedation is usually necessary. Intravenous benzodiazepines with or without narcotics are usually sufficient. The patient should be positioned with his back vertical. In critically ill patients, decubitus position may be used to keep pleural fluid in most dependent position. Percussion note in such areas would be dull. After local anesthetic infiltration and cleaning the site, the needle is passed at the superior border of the rib to avoid intercostal nerve and vessels. Site of entry is usually at the 5th or 6th intercostal space in mid axillary line or the posterior axillary line.The wound is dissected with the dissecting forceps and a puncture is made once the depth level of parietal pleura is reached. A chest tube is now inserted held with a curved artery forceps , once inserted, it is pushed to at least 5 to

6 centimeters, then sutured in place. Air or fluid should be freely drained. If pneumothorax is the case then a negative pressure of minus 10 centimeters may be applied to the drainage system (Figs 11.7 and 11.8). Column of the fluid should move freely with respiratory movements. Exact placement should be checked by obtaining the chest radiograph. Use of trocar to place chest tube is controversial due to associated risk of perforation of lung tissue.

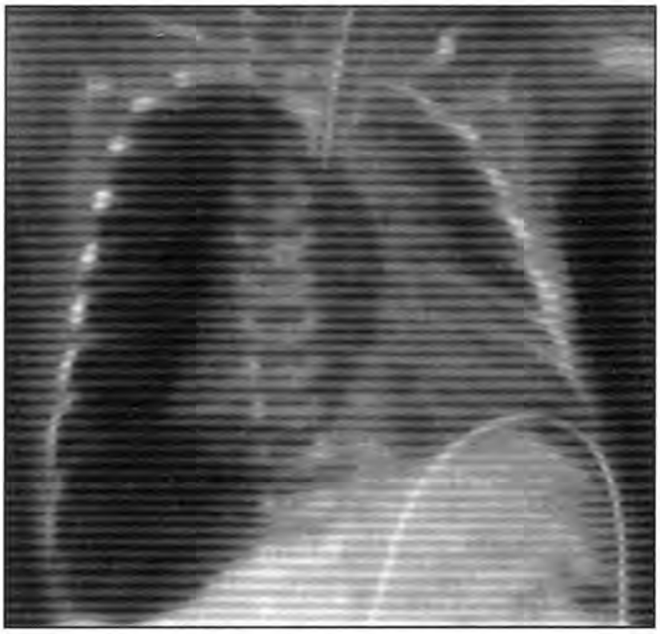


Fig. 11.7: Right pneumothorax on chest radiograph

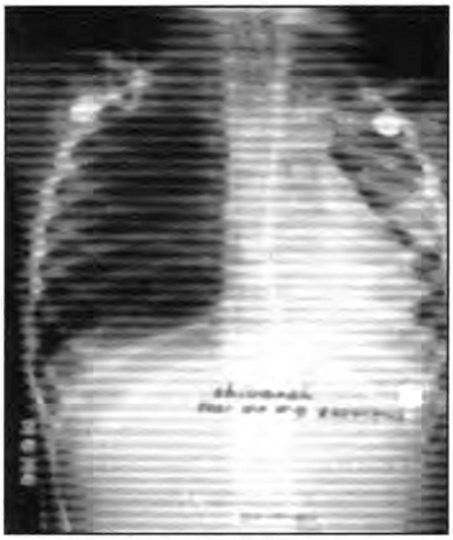


Fig. 11.8: Chest tube in place

Pericardiocentesis

Life-threatening pericardial tamponade by air or fluid is the main indication. In neonates pneumopericardium can be life-threatening in combination with pneumothorax as a part of acute air leak syndrome on mechanical ventilation for respiratory distress syndrome (Fig. 11.9).

Subxyphoid approach is used (Fig. 11.10). The needle (16 or 18 guage cannula) is introduced from right subxyphoid area pointing upwards towards the left nipple under all aseptic precautions. Only experienced persons should attempt this procedure.

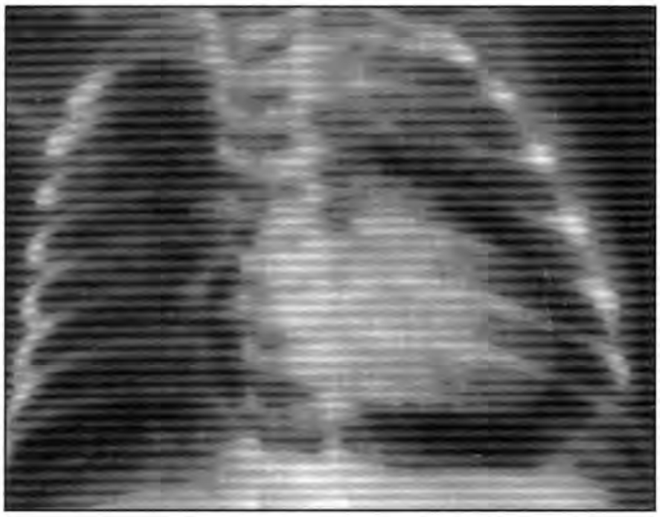


Fig. 11.9: Pneumopericardium

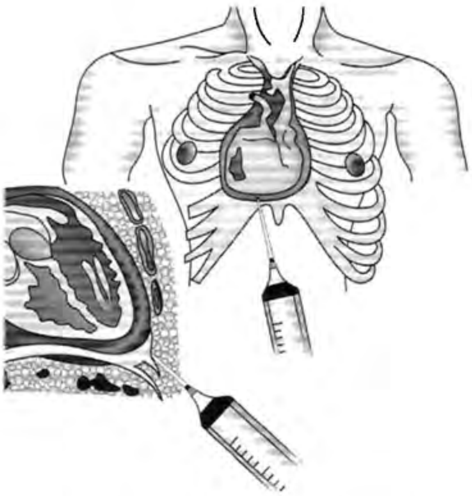


Fig. 11.10: Pericardiocentesis

Echocardiographic or fluoroscopic guidance may be necessary if placement of the pericardial catheter is required. Resuscitation cart and defibrillator must be available on standby.

The needle is advanced until the fluid is obtained. The cannula can now be advanced and the needle removed. A 30 or 60 cc syringe with a three-way stopcock may be used to drain air or fluid. After the pericardial tamponade is relieved, the improvement in signs and symptoms is immediate, heart rate, blood pressure and capillary perfusion improve significantly.

Cardiac dysrhythmias and myocardial injury are the main complications. These complications are easily treated by temporarily abandoning the procedure and mechanical irritation of myocardium.

ABDOMINAL PARACENTESIS

It is a percutaneously performed procedure for sampling and drainage of peritoneal cavity in patients with ascites, peritonitis or blunt abdominal trauma.

Indications

Therapeutic indications of this procedure include increase in intra abdominal pressure causing significant respiratory distress, cardiovascular compromise, oliguria, acidosis or raised intracranial pressure. In the pediatric ICU common therapeutic indications tend to be massive ascites, post fluid resuscitation with shock (especially meningococcemia, viral hemorrhagic shock such as Dengue shock syndrome), trauma, severe burns and multiple organ dysfunction with cumulative positive fluid balance.

Diagnostic indications include new onset ascites, chronic ascites with clinical deterioration and suspected peritonitis, pancreatitis and intraperitoneal bleeding. Diagnostic peritoneal lavage is not routinely recommended in evaluation of patients with blunt trauma due to high false negative rates[12], and due to easy availability of CT scan, which is non-invasive and provides more organ specific information helping with decision making of surgical intervention. Other rare indications include necrotizing enterocolitis. Various causes of ascites include portal hypertension, inferior vena caval obstruction, heart failure, nephrotic syndrome, lymphomas, leukemias or neoplasms involving liver or mediastinum, chronic pancreatitis, or cirrhosis o liver. A differential diagnosis of clinical symptomatology related to ascites is shown in Table 11.3.

Contraindications

There are no absolute contraindications to this procedure.

Paracentesis should be avoided in patients with acute abdomen who require immediate surgery Both coagulopathies and thrombocytopenia are considered as relative contraindications,therefore caution is necessary, however, prophylactic use of platelets or fresh frozen plasma for performing this procedure is not recommended.

Special caution is necessary in patients with severe bowel distension, history of previous abdominal or pelvic surgery, distended bladder that can not be emptied by foley catheter. Insertion sites where abdominal scar or cellulitis is apparent should be avoided due to possibility of adherent bowel or introduction of infection respectively. In pregnant

Table 11.3: Differential diagnosis of fluid in abdomen

Tender ascitis
Peritonitis
Pancreatitis
Congestive heart failure
Constrictive pericarditis
Biliary peritonitis
Hepatitis
Budd chiari
Intraperitoneal bleeding (trauma, ectopic pregnancy)
Hepatic abscess

Nontender ascitis with Low serum albumin
Protein losing enteropathy
Nephrotic syndrome
Malnutrition
Portal hypertension
Congenital syphilis
Cirrhosis

Nontender with normal serum albumin
Portal hypertension
Tubercular peritonitis
Chylous ascitis
Renal
Leukemia
Hodgekins lymphoma
Obstructive uropathy
Wilsons disease
Hematocolpos

patients paracentesis is relatively contraindicated but when necessary, it can be performed with insertion site supra umbilical and lateral to the midline.

Risks

It is a relatively safe procedure, however, following are some of the potential risks : Perforation of bowel, bladder, persistent leakage of fluid, intra abdominal bleeding, introduction of infection, and hypovolemic shock.

Technique

Paracentesis kits are usually available. Supplies usually needed for the procedure are listed in Table 11.4.

Table 11.4: Equipment for abdominal paracentesis

Skin cleansing solution (Povidone iodine, 70% alcohol)
Sterile gloves and mask
Sterile towel/drape
Local anesthetic 1% lidocaine with or without epinephrine
3-10 ml syringe with thin needle (25 gauge) for anesthesia
16,18 or 20 G angiocatheter (catheter over the needle)
20-22G needle for smaller children
16-20G needle for larger children.
20 ml syringe
60 ml syringe
Three way stop cock
Specimen vials
Sterile gauge dressing with tape or adhesive strip

Clinically diagnosis of ascites should be confirmed by shifting dullness, flank dullness and fluid waves performed on the child. Clinical exam will usually pickup patients with moderate to severe ascites, but some patients with mild to moderate ascites may be missed. Abdominal Ultrasound can detect even small quantities of fluid (as low as 150 ml), and should be used to help diagnose as well as to perform ultrasound guided aspiration to increase efficiency. Informed consent should be obtained after explaining the potential risks and benefits of the procedure to the parent. Older children should be explained the procedure and will usually cooperate. Sedation is usually required for younger children, discussed elsewhere.

In ascites, bowel tends to float in the non-dependent midline area. Therefore area of needle insertion should be dependent and lateral in children.

Patient should be placed in supine position with head elevated. Bladder should be empty. After gown and gloves are worn, the insertion site is prepared with povidone iodine or chlorhexidine followed by 70% alcohol. Skin is Infiltrated with local anesthetic solution. Preferred insertion site is 2 cm below the umbilicus in midline. Alternatively lateral insertion can be done preferably on left lower quadrant few centimeters above the inguinal ligament lateral to rectus abdominis muscle. A Z track method can be applied by placing caudal traction on skin after the needle has been inserted perpendicular to abdominal wall. This prevents the fluid leak thru the direct linear track, if Z track method is not used.

Once the appropriate sized needle(or angiocatheter) has been inserted, negative pressure is maintained with syringe and the needle is advanced further until a pop is felt as the needle enters the peritoneal cavity and free fluid is aspirated. If a catheter over the needle(angiocatheter)is used, the catheter can now be advanced over the needle into the peritoneal cavity and the needle is removed. 20-30 ml of fluid is usually enough for diagnostic studies, but for therapeutic drainage more fluid may be required until the abdomen is visibly lax and patients respiratory distress improves. Ascitic fluid may be sent for cell count with differential count, specific gravity, glucose, total protein, alkaline phosphatase, albumin, amylase, LDH, ammonia, creatinine, potassium, bilirubin, triglycerides, cellular morphology, aerobic and anaerobic cultures, viral, fungal cultures, acid fast bacilli stain and culture, and gram stain, as clinically indicated. Corresponding serum chemistries should also be sent. As a word of caution large volume drained quickly can result in shock and hypotension, therefore no more than 15-20 ml/kg should be drained at one time. Positional change may be necessary to facilitate drainage of the ascitic fluid. Pig tail catheter may be used if the drainage is needed over the next 24-48 hours leaving the catheter *in situ*, as indicated. After the removal of needle or the catheter, sterile pressure dressing should be applied.

Complications

Rate of complications is reported as 1-3%. Complications include bowel, bladder perforation, bleeding, subcutaneous hematoma, infection, persistent leak, scrotal edema or hypotension. Perforation of bladder can be prevented if care is taken to empty the bladder prior to procedure. Since chances of perforation of bowel is high in patients with history of previous surgery and adhesions, this can be prevented by avoiding old scars as the insertion site to prevent injury to adherent bowel loop.

Perforation of bowel will usually close quickly without leak unless intraluminal pressure is high. Perforation of blood vessel may result in bleeding. The bleeding usually stops quickly unless portal hypertension or severe coagulopathy is present. Perforation of solid organs can occur but usually bleeding will stop spontaneously. Introduction of infection into the peritoneal cavity is possible, therefore strict aseptic technique should be used. Scrotal edema (or labial edema in females) has been reported in patients with massive ascites and use of small needles can prevent it. Persistent leak of ascitic fluid is rare but usually responds to pressure. Use of Z track method usually prevents it. Hypovolemic hypotension can occur if more than 20 ml/kg fluid is aspirated from the peritoneal cavity.

Interpretation

Appearance

The fluid is normally straw colored. Turbid fluid is obtained in chemical or infectious peritonitis. Chylous ascites will yield milky or yellowish fluid. Bile stained fluid may be associated with pancreatitis or gall bladder or common bile duct perforation. Blood tinged fluid is seen with visceral disruption or traumatic tap.

Cell Count

In peritonitis >100000 red blood cells/ml or 500 white blood cells/ml with greater than 50% polymorphoneuclear cells will be seen. Lymphocytes will predominate with chylous ascites or tubercular peritonitis. If paracentesis is used to diagnose the need for surgery in necrotizing enterocolitis, 0.5 ml of brownish fluid indicates perforation or necrotic bowel. If gram stain reveals bacteria, patient needs surgery for necrotizing enterocolitis.

Chemistry

Low glucose is seen with bacterial or tubercular peritonitis. Glucose < 60 mg/dl is considered low or less than 2/3rd of serum glucose. Total protein < 2.5 g /dl, a fibrinogen level 0.3-4% of total protein, a fluid to serum protein ratio of less than 0.5 are consistent with a transudate. Specific gravity < 1015 is consistent with transudate. Alkaline phosphatase is greater than twice the serum level in patients with perforated or necrotic viscus. Ammonia level is twice as high compared to serum ammonia in patients with strangulated bowel and duodenal perforation. Ascitic fluid amylase is greater than serum amylase in patients with pancreatitis, pancreatic pseudocyst, intestinal perforation or strangulation. In urinary ascitis, ammonia creatinine and potassium will be elevated.

Serum Ascitic albumin gradient (SA gradient) is defined as the difference between serum and ascitic fluid albumin. SA gradient of 1.1gm or higher correlates with portal hypertension.

Ascitic Fluid Composition in Different Types of Ascitis

Spontaneous bacterial peritonitis: > 250 cells/ml, total protein 1 gm/dl. LDH and glucose may be normal. pH may be low or normal. Culture and gram stain may be negative. SA gradient is usually > 1.1 gm.

Secondary bacterial peritonitis: Total protein is >3 gm/dl, LDH is greater than serum LDH, Glucose is <50 mg/dl, > 500 cells/ml with polymorphonuclear predominance, gram stain is positive and SA gradient is <1.1 gm/dl. pH is not a reliable correlate of bacterial peritonitis.

Chylous ascitis: The fluid is usually milky, but it could be yellow or even clear. Cell count is 1000-5000/cu ml with lymphocytic predominance. Tryglyceride level is much higher than serum triglycerides (>1500 gm/dl). Total protein is < 3 gm/dl.

Pancreatic ascitis: Turbid, tea colored or bloody. Total leucocyte count and protein is raised. Amylase and lipase are higher than serum levels, however in patients younger than 4-6 months of age amylase may be low but lipase is always higher.

Tubercular ascitis: Bloody, yellow, firm clots. Total protein is >2.5 gm/dl. Leukocytes>1000cells/ml with predominant lymphocytes. Glucose is <30 mg/dl.

Urinary ascitis: Protein is <1 gm/dl, potassium and creatinine is higher than serum.

Malignant ascitis: Bloody fluid with increased proteins, LDH and low glucose, SA gradient is <1.1gm/dl

Nephrotic syndrome: Total protein is <2.5 gm/dl, fluid is essentially similar as in portal hypertension.

Biliary ascitis: fluid is bile stained. Bilirubin is much higher than serum bilirubin(100-400 mg/ml).

TRANSURETHRAL BLADDER CATHETERIZATION FOR INTRA-ABDOMINAL COMPARTMENT PRESSURE MEASUREMENT AND URINARY DRAINAGE

Transurethral Bladder Catheter Placement

In PICU transurethral bladder catheter placement is a commonly performed procedure as an integral part of strict intake and output monitoring of fluid balance, and lately its being used in certain specific situations for monitoring intra abdominal pressure. Various indications for placing a transurethral bladder catheter are as follows:

Indications

Shock
Acute urinary retention
Comatose patient
Multiple trauma
Severe head trauma
Obtain urine specimen for diagnosis
Measurement of intra-abdominal pressure

Risks

The procedure can usually be safely performed. Major risks include urethral trauma, bleeding and urinary tract infection.

Contraindications

Urethral trauma, or blood at the tip of meatus
Prostatic displacement on rectal examination(Male)
Obvious pelvic fracture
Perineal hematoma

Various catheter sizes are available as shown in Table 11.5. As a general guideline, an 8 french balloon tipped catheter can be placed in an infant, 10 french catheter in most children and 12 french catheter in older children. In the newborn age group, 8 french balloon tipped catheter may be difficult to pass and therefore 3-5 french feeding tube in male, 5 french feeding tube in the female new borns is generally recommended. Straight single lumen catheters and feeding tubes in sizes 8 and 10 are also available for newborns.

Table 11.5: Recommended catheter sizes for children

Age	*Boy (french size)*	*Girl (French size)*	*Type*
New born	3	3 or 5	Straight
1-2 yrs	5	5 or 8	Straight/balloon tipped
3-5 yrs	8	8	Balloon tipped
6-10 yrs	8 or 10	8 or 10	Balloon tipped
12 yrs	10 or 12	12	Balloon tipped
13 yr and older	12	12or 14	Balloon tipped

It is also important to use the guidelines for approximate length of urethra (Table 11.6) to prevent inserting excessive length of the catheter into the bladder resulting in knotting of the catheter.

Table 11.6: Approximate urethral length

Age	*Boy (cm)*	*Girl (cm)*
New born	6+/–2	1.5 - 2
2 yrs	8+/–2	1.5 -3
5 yrs	10+/–2	1.5-3+/-2
10 yrs	12+/–2	1.5-3+/-2
12 yrs	16-20+/–2	4-6+/-2

Equipment

Bladder catheter tray
Type and appropriate size of catheter
Gloves
Sterile drape
Povidone iodine
Absorbant cotton balls
Forceps
Lubricant jelly
10 ml prefilled inflation syringe
Sterile specimen container and labels
Drainage tube and bag

Technique

Knowledge of male and female anatomy is important to successfully perform this procedure.One assistant is usually required for help with restraining and for maintaining sterility.

Catheter tray equipment needs to be arranged. Sterile drape is opened and placed near the genital area. Using sterile technique wearing the gloves, catheter is opened and dropped on to sterile drape. Lubricant jelly is also placed on sterile drape. Sterile basin and specimen containers are also placed on the drapes.

Have assistant provide gentle restraint if young patient. Older children can usually cooperate if the procedure is explained beforehand.

Povidone iodine wipes are opened. In female patient labia majora is separated with thumb and index finger. Urethral meatus is swabbed from front to back three times with separate swabs.

In male, foreskin is retracted with thumb and index finger of left hand and if necessary meatus and glans is exposed, penis gently extended and the area of penile urethra is cleaned three times with separate povidone iodine swabs.

While maintaining this position, catheter tip is lubricated with the right hand and the distal end of catheter is placed in sterile container to collect urine.

Catheter is now inserted into the meatus of urethra and pushed until urine appears at the other end of the catheter. Catheter should be advanced further to enter the bladder as urine may appear while the tip of the catheter is in urethra. Urine specimen can now be collected in the sterile container.

Force should not be applied if resistance is felt. In males slight traction of penis may help in smoother entry into the bladder. In female patient if catheter enters vagina by mistake, it should be discarded and new catheter should be inserted to prevent contamination of the urine.

In older children, 1 ml of urine should be discarded to avoid a contaminated specimen. Balloon tip should now be inflated with the prefilled syringe locked to the port on the catheter for inflation. Once inflated, the catheter is gently pulled until resistance is met or one gets the klunking sensation. This indicates that the catheter is firmly placed sealed with the balloon tip near the bladder meatus. End of the catheter should be wiped with povidone iodine and connected to the tubing of the urine bag. Catheter can now be taped to the inner thigh leaving some slack allowing for leg movement. In neonates one should use the tape on the feeding tube to proximal inner thigh. In males tape should be around the feeding tube and along the penile shaft to secure the tube properly.

Complications

Following complications have been reported:
Urethral, Bladder trauma
Vaginal catheterization
Urinary tract infection
Intra vesical knott
Paraphimosis
Hematuria

Most of these complications can be avoided by careful handling of the catheter and following the guidelines for appropriate sizes and lengths of the catheters used. A catheter change at regular intervals (varies from 72 hours to 7 days in pediatric ICUs) in patients needing long term urinary drainage, may reduce the incidence of nosocomial urinary tract infections.

Intra Vesical Pressure Measurement for Abdominal Compartment Pressure Measurement

It involves the measurement of bladder pressure for measurement of intra abdominal pressure (IAP) to detect intra abdominal hypertension (IAH), leading to abdominal compartment syndrome (ACS).

Though knowledge of IAH dates back to late 1800s, ACS was first described in adults, its pathophysiology and effects on renal function and cardiovascular function have been well-described. One of the earlier reports of increased IAP was from children with omphalocele. It was rediscovered in 1989 as a complication of ruptured abdominal aortic aneurysm repair. Subsequently various reports from adult trauma literature followed and recently many pediatric reports have been published suggesting the importance of monitoring of IAP in an attempt to pick up IAH early, intervene and hopefully prevent associated complications.

Common clinical situations where IAP can increase include trauma leading to accumulation of blood, fluid or edema. Non-traumatic bowel ischemia, infarction or gastrointestinal hemorrhage can lead to similar situation due to edema or fluid collection. Common scenario in the pediatric ICU involves a child with septic shock with capillary leak (Meningococcemia, viral hemorrhagic fever with or without clinical bleeding), multiple organ dysfunction syndrome (MODS) with fluid overload and oliguria, ischemia reperfusion injury following fluid resuscitation in trauma, severely burned patients, post liver transplant, post-abdominal surgical closure of abdominal wall defect (gastroschiesis or omphalocele).

Due to resulting increase in IAP, this can lead to inferior venacaval compression, reduction of thoracic venous return and cardiovascular compromise, leading to further oliguria, due to poor renal perfusion and metabolic acidosis. Arterial occlusion can occur due to raised IAP. In addition respiratory compromise due to impaired diaphragmatic excursion, raised airway pressures and reduction of pulmonary blood flow leads to hypoxemia and hypercarbia. Abdominal tamponade leads to increased intracranial pressure and reduction in cerebral perfusion pressure. Abdominal perfusion pressure (Mean arterial pressure—intra-abdominal pressure) is reduced leading to organ ischemia and further deterioration of multi organ dysfunction. Early monitoring of IAP is recommended in certain specific situations where the patient is at high risk of getting ACS or is already exhibiting signs of ACS.

Indications for Intra-abdominal Pressure Measurement

Though specific pediatric indications are not established in literature but based on currently available information following indications may apply.

Patients at Risk for Developing ACS

Blunt injury abdomen
Mechanically ventilated patients with MODS
Meningococcemia
Dengue shock syndrome
Severe burns
High cumulative fluid balance
Postoperative patients with abdominal packing

Patients with Signs of ACS

Abdominal distension, oliguria, hypoxia, hypotension, acidosis, elevated intra cranial pressure

Though various techniques of intrabdominal pressure monitoring including intragastric pressure and intravesical pressure have been described, measurements of intravescical pressure is considered as a gold standard for IAP measurement.

Technique for intravesical pressure measurement was first described by Kron, validated by Iberti, later modified by Cheatham. Recently there have been reports suggesting the inaccuracy of clinical examination in detecting IAH and a need for standardization and development of clinical practice guidelines for adults. Though measurement of IAP has been recommended in pediatric patients with abdominal wall defects and children with major burns, routine measurement of intra abdominal bladder pressure is not yet a common practice the pediatric ICUs. In pediatric patients, various indirect methods to measure intravesical pressure have been compared recently.

Equipment

Bladder catheterization equipment (see transurethral bladder catheterization)
Appropriate sized balloon tipped bladder catheter
Transducer set up and tubing
Pressure module/monitor
Normal saline bag
60 ml syringe
Threeway stopcocks
Tubing clamp
The setup is schematically shown in Figure 11.7.

Technique of Intravesical Pressure Monitoring

Following is a description of a practical technique of bladder pressure measurement based on the technique described by Kron and Cheatham.

One needs to ensure the presence of a catheter with closed system drainage in place. Patient is placed in supine position. After washing hands and wearing gloves transducer system should be

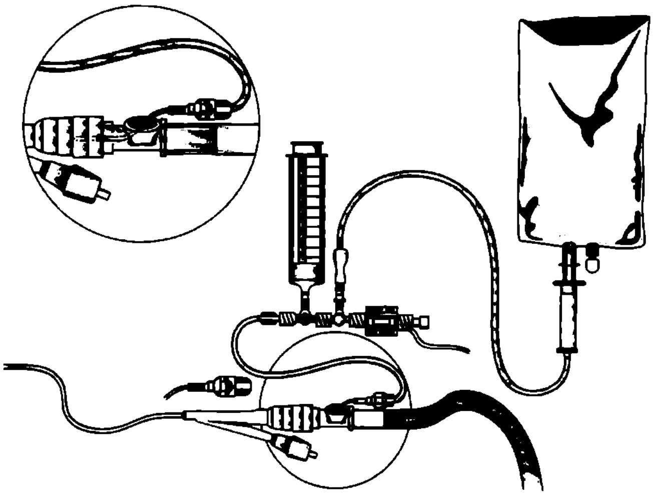


Fig 11.7: Cheatham technique of intra-abdominal pressure measurement

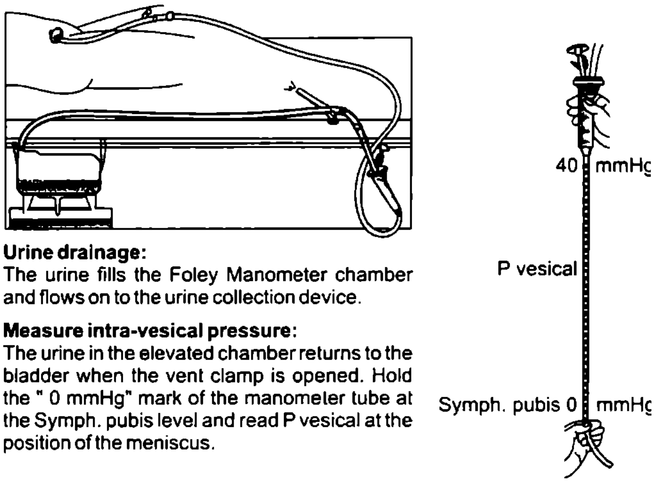
connected to the monitor with connection to the pressurized bag. A 30 mm or 60 mm scale should be selected. A 60 ml syringe is attached to the distal stopcock as shown.

Symphysis pubis is taken as zero reference point. Bladder drainage system is now clamped just distal to the catheter and drainage bag connection on drainage bag tubing.

Sampling port of the catheter is now cleaned with povidone iodine swab. 18 G or 16 G needle is now inserted in the sampling port as shown. Stopcock attached to the syringe is turned off to the patient. Pressure bag is now open towards the syringe and by fast flush system (pigtail) the syringe is filled to 50 ml by pulling on the plunger. Stopcock is now turned off to pressure bag and open to syringe and the patient. 1 ml/kg saline is injected into the bladder. Some recommend 30-50 ml Normal saline to be injected for most patients. Any air seen between the clamp and the urinary catheter is expelled by opening the clamp and allowing the saline to flow back past the clamp and then the tubing is reclamped. A strip of pressure wave form is run which tends to show small variation between inspiration and expiration; end inspiratory pressure on the waveform is taken as intraabdominal pressure. Once the pressure measurement has been made, the needle is removed from the sampling port and catheter drainage tubing is unclamped. Amount of saline injected should be accounted for in the output charting.

Alternative Method: If transducer is not available catheter tubing is simply raised vertically above symphysis pubis at a 90 degree angle to the patients pelvis and tubing is unclamped. The distance in cm between the symphysis pubis zero point and the maximal height of the fluid column is recorded. This minimally invasive technique is popular in some institutions because it is quick and can be easily performed by the staff without the need for a transducer set up.(Fig. 11.8).

To maintain a closed drainage system, without having to use a needle to connect to the sampling port of the catheter, a valve (AbViser, Wolfe Tory Medical Inc, Salt lake city, Utah) is now available to place at the drainage port of the catheter. As shown in Figure 11.9, this valve has two positions, in the first position it is connected to the urinary drainage system and in the other position (changed by rotating mechanism) it gets in line with the transducer system, whenever bladder pressure measurement is required.


40 mmHg
P vesical
Symph. pubis 0 mmHg

Urine drainage:
The urine fills the Foley Manometer chamber and flows on to the urine collection device.

Measure intra-vesical pressure:
The urine in the elevated chamber returns to the bladder when the vent clamp is opened. Hold the " 0 mmHg" mark of the manometer tube at the Symph. pubis level and read P vesical at the position of the meniscus.

Fig. 11.8: A simplified method to measure bladder pressure (P vesical) if the transducer system is not available

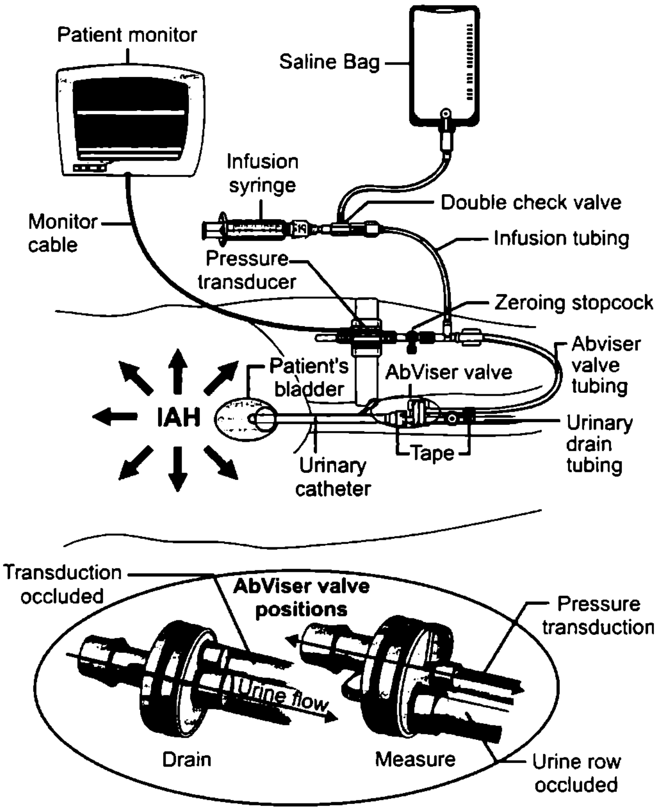

Patient monitor
Saline Bag
Infusion syringe
Double check valve
Monitor cable
Infusion tubing
Pressure transducer
Zeroing stopcock
Abviser valve tubing
Patient's bladder
AbViser valve
IAH
Urinary drain tubing
Tape
Urinary catheter
Transduction occluded
AbViser valve positions
Pressure transduction
Urine flow
Drain
Measure
Urine row occluded

Fig. 11.9: ABV200 Pediatric Intra-abdominal pressure monitoring kit (Wolfe Tory Medical Inc) (Salt lake city, Utah)

Interpretation of Intra-abdominal Pressure and Interventions

Pediatric normal values are not established for IAP. Based on adult data normal range of IAP is 0-12 mm of Hg. IAH is defined as an IAP >12 mmHg. ACS has been said to occur with IAP of > 20 mmHg. Severity of IAH has also been described as mild (10-20 mmHg) moderate (>20-40 mmHg) and severe (>40 mmHg). Incidence of ACS is 15% in adult studies, much higher compared to pediatric incidence of 0.7% in 1762 patients with mixed medical surgical population over a 5 year period and an incidence of 0.6% in 406 trauma patients. It is possible that due to lack of awareness among the pediatric intensivist as well as non reliability of clinical examination to detect ACS, in children, diagnosis of significant IAH may get missed. It is reasonable to keep a high index of suspicion in patients at risk for developing ACS and measurement of IAP instituted early during the course of illness.

Various interventions that have been recommended to reduce IAP range from gastric suction, enemas, diuretics, muscle relaxants to paracentesis or surgical decompression as clinically indicated. Because level of IAP at which ACS occurs in children is unknown some have suggested that a distended abdomen, oliguria and/or hypoxia and hypercarbia plus increase airway pressure justify abdominal decompression. One pediatric study showed that decompression done in children at IAP as low as 17 mm Hg led to clinical improvement, though overall mortality was high at 60%, suggesting an even earlier intervention to reduce IAP may have been beneficial. Some authors have recommended decompression at >25 mm Hg in three patients treated by silo decompression. Paracentesis may provide an alternative to operative intervention in pediatric patients with severe traumatic liver injuries and ACS related to fluid and blood accumulation.

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CHAPTER

12

Flexible Bronchoscopy in Infants and Children

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Flexible fiberoptic bronchoscopy in children and infants is now recognized and accepted as a diagnostic and, to a certain degree, therapeutic modality.

In the late 1970s, Robert E. Wood began promoting the direct examination of the tracheobronchial tree with specially constructed, flexible fiberoptic bronchoscopes (FFBs) suitable for use in infants and children. He is clearly responsible for laying foundation for pediatric flexible fiberoptic bronchoscopy (PFFB), and the training program. This greatly facilitated the use of technique and aided diagnosis and management of various disorders of respiratory tract including vocal cord palsy, laryngo tracheomalacia, laryngeal web, subglottic stenosis, tracheal stenosis, tumors, inflammatory lesions, tuberculosis, foreign bodies and recurrent atelectasis. In addition to diagnosis of various disorders PFFB has been instrumental in the following areas:

1. Inspection of airways, primarily the trachea, before decannulation of tracheostomy tube or a change of tracheostomy tube to a smaller or larger size as clinically indicated.
2. In cases of severe tracheomalacia, the FFB is used to measure the exact length from the tracheostomy skin stoma to carina. This enables ordering a custom-made tracheostomy tube with specified dimensions (Bivona or Shiley) that could serve as an effective stent.
3. Measurements and photographic recording of tracheal and main-stem bronchi diameter is possible with the ultrathin FFB as levels of positive end expiratory pressure, bilevel positive airway pressure, or continuous positive airway pressure are adjusted.
4. Guiding life-saving or difficult intubations in cervical traumatic injuries, or other conditions with difficult airway, as well as confirming patency or position of the endotracheal tube.
5. Perform bronchalveolar lavage as well as transbronchial biopsies.
6. Perform the diagnosis and in some cases removal of foreign bodies.
7. Placing tracheal or bronchial stents in patients with tracheobronchmalacia.

In this part of the world PFFB is being used both as an out patient and an inpatient procedure for diagnostic and therapeutic purposes, mostly by pediatric pulmonary specialists, pediatric intensivists and pediatric anesthesiologists (for difficult intubations). Rigid bronchoscopy is mainly performed by pediatric surgeons, thoracic surgeons and pediatric ENT specialists.

This text has been written with a purpose to familiarize reader with the indications and technique of FFB in neonates and pediatric age group. The equipment available for this purpose and its maintenance, sedation and anesthesia, post procedural care and complications are discussed. Techniques of use for airway inspection, bronchalveolar lavage, transbronchial biopsy, foreign body removal and airway stent placement have also been described.

Practical use of FFB can only be learned by practice on airway models, anesthetized animals (monkey), observation of the procedure performed on the patients by the expert bronchoscopist. Once initiated, the technique can be gradually mastered. Training programs and workshops for FFB are available in Cincinnati(USA) by Dr Robert Wood as well as in India conducted by IAP(Indian academy of pediatrics) respiratory chapter.

INDICATIONS

Most common indications of flexible fiberoptic bronchoscopy (FFB) in pediatrics are those related to either upper or lower airway obstruction including stridor, noisy breathing, snoring of uncertain anatomic origin, or atypical wheeze. Stridor is one of the most common indications for bronchoscopy in children. Vocal cord dysfunction can often be diagnosed on clinical grounds or via spirometry, but the visual identification of vocal cord abduction with the patient conscious and viewing the video screen can be helpful, both from diagnostic and therapeutic points of view. Suspected aspiration of gastric contents or feedings due to swallowing dysfunction appears to be reasonably common in the population seen by most pediatric pulmonologists. Flexible bronchoscopy is commonly performed as part of the evaluation to inspect the airway and perform BAL to evaluate for lipid-laden macrophages, or bacteriological studies.

The decision to perform FFB in children is made depending on the patient's history, physical examination, and the results of previous diagnostic tests. FFB can be performed for diagnostic and therapeutic purposes or in order to obtain secretions and cells from the lungs. FFB is generally contraindicated for the treatment of massive hemoptysis, and in the diagnosis of acute epiglottitis. Indications for diagnostic bronchoscopy vary with the age of the patient. In children a normal bronchoscopic examination can be of be as important as a specific finding, because it definitively excludes suspected problems such as foreign body aspiration. The diagnostic yield of FFB can be increased by the information obtained with bronchoalveolar lavage (BAL) and biopsy of the mucosa.

The evaluation of airways obstruction, which may involve the upper or lower airway or both, is the most common indication for FFB in children. Stridor or noisy breathing (due to obstruction of the upper airways) is the most common indication for FB in infants. Nasal insertion allows the examination of the adenoids, and the larynx and hypopharynx in the most physiological conditions and often when the stridor is audible. This allows study the laryngeal structure and function during inspiration and expiration. Dynamic obstruction caused by laryngotracheomalacia can also be assessed adequately. Table 12.1 shows indications of pediatric FFB (Figs 12.1 to 12.4).

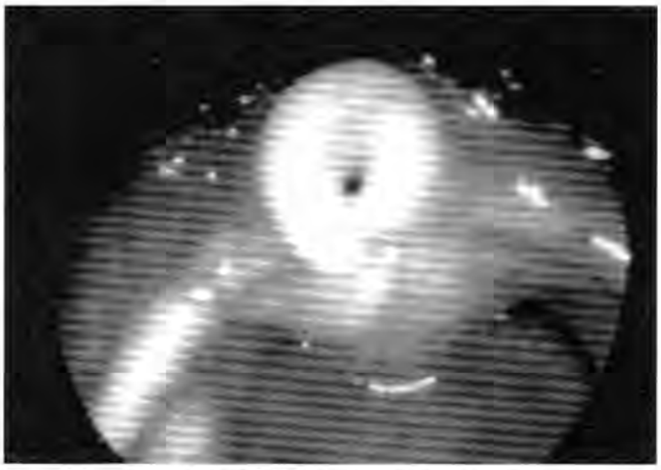


Fig. 12.1: Laryngomalacia

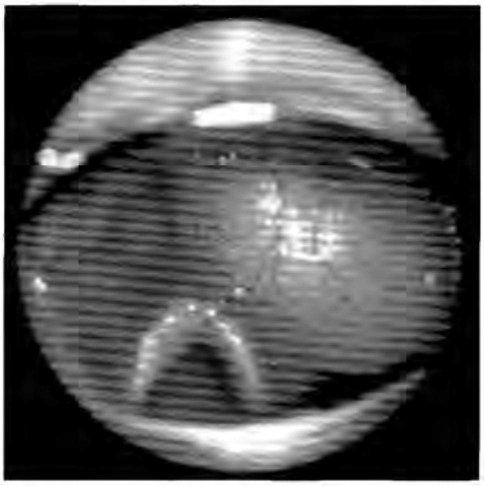


Fig. 12.2: Epiglottic cyst

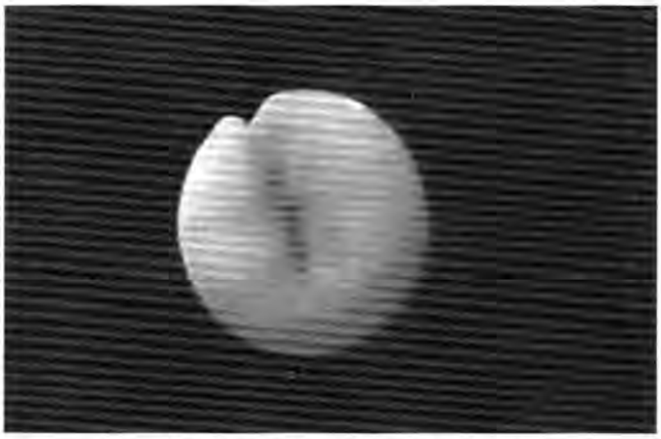


Fig. 12.3: Extrinsic bronchial compression
(For color version see Plate 4)

The most common congenital laryngeal anomaly and the most frequent cause of persistent stridor in children is Laryngomalacia. Other congenital anomalies of the larynx causing stridor are laryngoceles and saccular cysts, laryngeal webs and atresia, laryngotracheal stenosis, laryngeal and tracheal clefts, congenital neoplasms such as hemangiomas, bifid epiglottis and ventral cleft of the larynx. Laryngeal cleft may be missed by FFB, and rigid bronchoscopy performed if this diagnosis is seriously considered. Paralysis of the vocal cords is the third most common congenital laryngeal anomaly producing stridor in infants and children and it is usually the result of congenital anomalies of the central nervous system.

Table 12.1: Indications for pediatric flexible bronchoscopy

Airway obstruction
Stridor/noisy breathing
Persistent/recurrent wheezing
Radiographic abnormalities
Atelectasis
Recurrent/persistent consolidations
Atypical and unknown infiltrates
Localized hyperinflation
Chronic cough
Suspected foreign body aspiration
Hemoptysis
Evaluation of the artificial airway
Therapeutic bronchoscopy
Restoration of airway patency
Mucus plugs or blood clots
Alveolar filling disorders (alveolar proteinosis, lipid pneumonia)
Special procedures
Bronchoalveolar lavage
Brushing or biopsy of the bronchial mucosa
Biopsy of endobronchial lesions
Transbronchial biopsy
Administration of drugs
Endoscopic intubation

Although there is insufficient data on the frequency of concomitant abnormalities, abnormalities below the epiglottis were found in up to 68% of cases. Wood reported that in 15% of children examined for stridor and in whom a plausible explanation for the stridor was found at the subglottis or above, there was an additional lesion in the trachea or bronchi. So unless there is a good reason not to do so, a thorough examination of both the upper and lower airways should be done whenever a bronchoscopy is done. Therefore, if possible, it is important to inspect both the upper and lower airways in any case of airway endoscopy. Although bronchoscopy is not necessarily indicated in every infant with stridor, it should be performed in any child with severe or persistent symptoms, if associated with hoarseness or if it leads to oxygen desaturation or apnea.

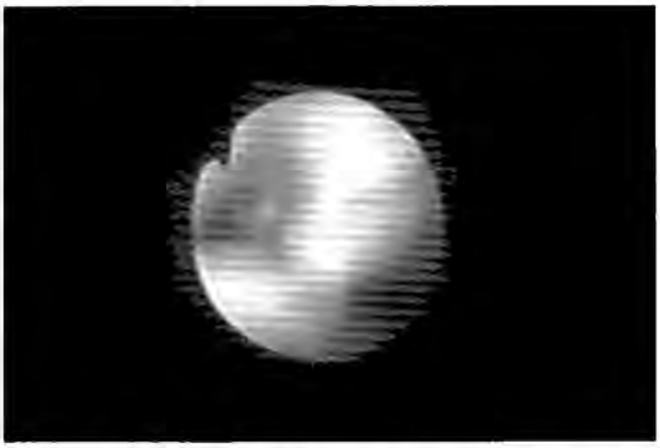


Fig. 12.4: Endobronchial Tuberculosis
(For color version see Plate 4)

Stridor is rare in older children, if not due to recent endotracheal intubation, is always an indication for endoscopy of the airways. Persistent/unexplained wheezing that does not respond to bronchodilator and anti-inflammatory therapy is another clinical indication for FFB, mainly in infants. It is often caused by congenital malformations of the tracheo-bronchial tree such as primary tracheomalacia and bronchomalacia, stenosis and webs of the trachea, tracheomalacia or bronchomalacia secondary to vascular compression, tracheoesophageal fistula or esophageal atresia, enlargement of the left atrium or congenital cysts.

Localized monophonic wheeze may be present in a child with foreign body aspiration. There are no controlled studies on the indications of flexible endoscopy in the literature, but airway abnormalities were found in 50% of cases in one series. It should be noted that FFB is superior to rigid bronchoscopy in the assessment of airway dynamics, because less positive end expired pressure is applied during the examination.

Complicated, severe, or persistent pneumonias and pneumonias in immunocompromized patients are other common indications for pediatric flexible bronchoscopy. Hemoptysis, undifferentiated lesions in the lung on chest radiograph, and non-infectious parenchymal lung diseases are all less common in children but still lead to elective fiberoptic bronchoscopy at times. When transbronchial biopsy is added to flexible bronchoscopy, the most common indications are those conditions in which histopathology is important in therapeutic decision making, such as lung transplantation and rare or unusual parenchymal lung diseases. Endobronchial masses are very rare in children except for foreign bodies and endobronchial tuberculosis. Foreign bodies are virtually always indications for rigid bronchoscopy in most institutions, although a recent data demonstrates excellent safety and efficacy record utilizing FFB with urologic baskets and forceps. A variety of radiographic anomalies represent important indications for FFB in children. Recurrent/persistent atelectasis, recurrent pneumonia, persistent pulmonary infiltrates or mass lesions are radiological indications for bronchoscopy.

Undetected foreign body aspiration, anatomic abnormalities and mucus plugs are commonly found. In these situations, it is also very important to perform BAL in order to obtain pulmonary samples for microbiological studies and to try to exclude clinical situations such as aspiration and interstitial lung diseases. Localized hyperinflation may be the result of partial bronchial obstruction and can be the consequence of foreign body aspiration, extrinsic bronchial compression and localized bronchomalacia.

Chronic cough both atypical and persistent in a patient with normal imaging, functional studies and hematological examinations, not responding to medical therapy is another indication for flexible endoscopy in children. It helps exclude foreign body aspiration and congenital malformation. A BAL should be performed to try to rule out microaspiration.

Suspected foreign body aspiration can be excluded with FFB, but it is recommended that foreign body extraction in children should be performed with the rigid bronchoscope. But many bronchoscopists are using FFB to remove foreign bodies with an acceptable success rate. Hemoptysis is a relatively uncommon indication for diagnostic bronchoscopy in children. However, hemoptysis associated with a clear episode of pneumonia should be evaluated with bronchoscopy in order to exclude the presence of a foreign body, malignancy or vascular malformation. Evaluation of an artificial airway (tracheostomy or endotracheal tube) is a common indication for diagnostic bronchoscopy.

Diagnostic flexible endoscopy is also indicated in infants and children with obstructive apnea.

The diagnostic yield for FFB will depend on the population studied, and the previous investigation and treatment performed. For example, the highest yields for BAL in the immunocompromized host will be before empirical treatment is started, and in patients not receiving prophylaxis for Pneumocystic carinii. There are no internationally agreed guidelines on the expected diagnostic yield for the procedure. Quantitative bacterial cultures of BAL have been used to diagnose pneumonia in immunocompromized and immunocompetent patients. When BAL with $<1\%$ squamous epithelial cells was analyzed, the finding of $>10^5$ colony-forming units of a single bacterial species per ml of BAL was correlated with bacterial pneumonia in comparison with normal subjects (Table 12.2).

Table 12.2: Flexible v/s rigid bronchoscopy

Flexible bronchoscopy	*Rigid bronchoscopy*
Advantages	**Advantages**
Relatively atraumatic as compared to rigid bronchoscopy	Excellent control of airway
Does not cause mechanical distortion	Use in upper airway obstruction
Inserted with head and neck in neutral position	Therapeutic (removal of foreign bodies and thick mucous plugs, interventional bronchoscopy)
Natural dynamics of the palate and larynx can be visualized	
	Disadvantages
Upper lobes easily visualized	Risk of trauma to the airway
Easy to perform bronchoalveolar lavage	Cannot be passed to the distal airways
Allows bronchoscopic intubations	Difficult to visualize upper lobe bronchi
Can be used in ventilated patients	
Disadvantages	
Partially occludes the airway	
Limited instrumentation (e.g. foreign body removal)	

In immunosuppressed patients with diffuse lung infiltrates, *P. carinii* can be identified in BAL with a sensitivity of up to 85%. Based on response to therapy or histology findings on biopsy or autopsy, the absence of *P. carinii* in BAL in immunosuppressed patients has a negative predictive value of >90%. In these patients, the sensitivity for detecting *M. tuberculosis* is up to 95%. The negative predictive value of absence of *M. tuberculosis* on BAL is >90%. The role of BAL in monitoring interstitial diseases and chronic infective disorders such as tuberculosis and cystic fibrosis is controversial and undefined for routine use. The small size of the working channel is one of the limiting factors for performing a Transbronchial lung biopsy(TBB) through the pediatric flexible bronchoscope. The dominant role of TBB is in interstitial lung disease and immunocompromized individuals including lung transplant recipients.

Furthermore, in assessing figures of diagnostic yield of an examination, it is important to differentiate diagnoses that are of importance to the child, and findings of mere curiosity value which do not alter management. The indications for therapeutic FFB primarily involve the restoration of airway patency.

Mucus plugs or blood clots in the airways causing atelectasis can be removed with the flexible bronchoscope. Most mucus plugging can be cleared by FFB; just occasionally, rigid bronchoscopy is needed to remove large resistant plugs. Patients with alveolar filling disorders, such as alveolar proteinosis or lipid aspiration may benefit from BAL through a flexible bronchoscope.

FFB can be used in order to perform special procedures such as biopsy of endobronchial lesions, biopsy and brushing of bronchial mucosa, transbronchial biopsy, bronchoscopic intubation and BAL. It is also a tool to administer drugs such as surfactant or deoxyribonuclease (DNase).

Airway problems may be the primary reason for admission to the pediatric intensive care unit (PICU), or arisen as a secondary complication of another illness. Children in PICU may be ventilator dependent, have hemodynamic instability or a coagulopathy. Evaluation of the endotracheal tube position or as an aid to the intubation of the difficult upper airway using a FFB is another reasonably common indication. Flexible bronchoscopes of appropriate size can be passed through the endotracheal tube or the tracheostomy in order to evaluate the patency or the position of the tube. Children who are not intubated should be managed as indicated above although it may be desirable to transfer them to operating room for the procedure to be undertaken under general anesthesia.

Children who are intubated and ventilated should be under full monitoring. Airway can be maintained using an endotracheal tube, a laryngeal mask or a facemask. In an unstable child, it is wise for the observer to limit the length of time the bronchoscope is down the airway to few seconds. Hypoxia is common particularly during BAL.

Contraindications

There are no absolute contraindications for flexible bronchoscopy. When the risk of the procedure outweighs the potential benefits, or when respiratory failure in a small infant will not permit the passage of a flexible bronchoscope while gas exchange is maintained, bronchoscopy should be deferred. The decision depends on the skill and experience of the bronchoscopist and clinical practice and the protocol followed by the department/center. Coagulopathy is a relatively strong contraindication to transbronchial biopsy. With use of laryngeal mask, more young patients may safely undergo bronchoscopy with ventilation.

Bronchoscopic Equipment

Currently four Japanese companies and one American company have produced bronchoscopes; over 95 per cent of these are made in Japan.

The flexible fibreoptie bronchoseope tip can be widely moved through an angle of 150-180°. This fibrescope is capable of an angle of viewing ranging from 55-120° at the tip; in addition, its visual image is strikingly clear in spite of using glass fibres. Therefore the old bronchoscope, which showed the proximal bronchus only, has been largely superseded; the new instrument alters the conception of bronchoscopy itself. It shows the area from the lobar bronchus to the fourth order subsegmental bronchi; it also helps the collection of specimens by using biopsy forceps or brushes and these specimens can be examined in a variety of ways.

Now the rigid bronchoscope, and the flexible fiberoptic bronchoscope are widely used for investigating various pulmonary diseases (Fig. 12.5). The use of the flexible fiberoptic bronchoscope has spread widely and the procedure using this instrument is now becoming routine for the pulmonologist, anesthesiologist, intensivist, otolaryngologist, and the surgeon.

Table 12.3 shows various sizes of pediatric flexible bronchoscopes that are available.

Table 12.3: Sizes of pediatric flexible bronchoscopes

External diameter (mm)	*Working channel*	*ET*Size +*	*Age group*
2.2	Nil	2.5-3.0	Premature and term infants
2.8	present	3.5-4.0	Term infants – 1 year
3.2-3.5	Present	4.0-5.5	Term infants – up to 7 years
4.5-4.9	Present	5.5-6.5	7 years and older

*ET—Endotracheal tube + Minimum endotracheal tube size through which the flexible bronchoscope can pass

Commonly available brands include Olympus, Storz, and Fujinon.

Olympus has developed a new line of bronchoscopes, the BF-60 series, for high-precision bronchoscopic examination and treatment by offering improvement in insertability; more width on the inside; and high image quality. Following is the description of the different types of scopes, each of them coming with a unique function. A cart with the videoscope is available to record and print bronchoscopic images (Fig. 12.6).

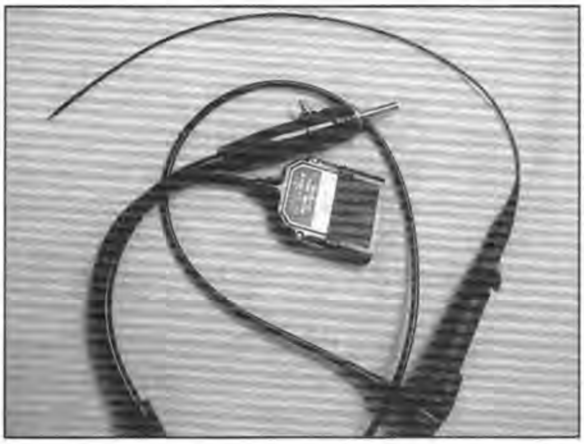


Fig. 12.5: Neonatal Bronchoscope *(For color version see Plate 4)*

Fig. 12.6: Bronchoscopic videoscope cart *(For color version see Plate 4)*

1. OLYMPUS BF TYPE P60 (Table 12.4)

The BF P60'S image guide has more optical fibers, producing sharper, smoother pictures. It has a wide 120° field of view that brings more of the target site into view. Its 180°up/130°down angulation makes it easier to maneuver the scope in the bronchi and accesses the target site. It is compatible with high frequency electro-surgical devices and with OES and EVIS video system. This scope is ideal for routine applications.

Table 12.4: Specification BFP 60

	Field of view	120°
	Direction of view	0° (Forward viewing)
	Depth of field	3~50 mm
	Distal end outer diameter	4.9 mm
	Insertion tube outer diameter	5.0 mm
	Working length	600 mm
	Channel inner diameter	2.2 mm
	Minimum visible distance	5 mm from distal end
Bending section	Angulation range	Up 180°, Down 130°
total length		900 mm

2. OLYMPUS BF TYPE 1T60 (Table 12.5)

This is equipped with an extra wide instrument channel measuring 3.0 mm across that can easily accommodate 2.8 mm diameter forceps and has increased suction power. It has a 120° field of view, 180°up/130°down angulation and a 600 mm working length, which enables accurate observation of a wider area and easy maneuverability in the tracheobronchial tree which enhances its therapeutic capability.

Table 12.5: Specifications BF 1T60

	Field of view	120°
	Direction of view	0° (Forward viewing)
	Depth of field	3~50 mm
	Distal end outer diameter	5.9 mm
	Insertion tube outer diameter	6.0 mm
	Working length	600 mm
	Channel inner diameter	3.0 mm
	Minimum visible distance	5 mm from distal end
Bending section	Angulation range	Up 180°, Down 130°
total length		900 mm

3. OLYMPUS BF TYPE MP60 (Table 12.6)

This scope measures only 4.0mm across the distal end and 4.4 mm at the insertion tube. This also incorporates a large 2.0 mm wide instrument channel able to accommodate standard forceps for use in peripheral lung biopsies. This has a wide 120° field of view and 180°up and 130° down angulation for easier for easy maneuvering in the bronchi and is an excellent choice for tracheo bronchial applications.

Table 12.6: Specifications BFMP60

	Field of view	120°
	Direction of view	0° (Forward viewing)
	Depth of field	3~50 mm
	Distal end outer diameter	4.0 mm
	Insertion tube outer diameter	4.4 mm
	Working length	600 mm
	Channel inner diameter	2.0 mm
	Minimum visible distance	3mm from distal end
Bending section	Angulation range	Up 180°, Down 130°
Total length		900 mm

4. OLYMPUS BF TYPE XP60 (Table 12.7)

This has an extra slim design that measures onl 2.8 mm across at both distal end and insertion tube and a reduced bending radius, which makes it abl to reach even the outermost peripheral bronchi Despite its ultra thin design, it incorporates ar instrument channel measuring 1.2 mm across. Also it has connectivity to OES and EVIS video systems

Table 12.7: Specifications BFXP60

	Field of view	90°
	Direction of view	0° (Forward viewing
	Depth of field	2~50 mm
	Distal end outer diameter	2.8 mm
	Insertion tube outer diameter	2.8 mm
	Working length	600 mm
	Channel inner diameter	1.2 mm
	Minimum visible distance	1.5 mm from distal end
Bending section	Angulation range	Up 180°, Down 130°
total length		910 mm

5. OLYMPUS BF TYPE 3C40 (Table 12.8)

This scope delivers excellent optical performance due to the use of extra fine optical fibers. Also, it has a slim design with the distal end measuring only 3.3mm across. These feature sallow the scope to penetrate even fur there into the bronchial tree and see more clearly as well. Its high-resolution images are bigger, sharper and clearer with reduced dot patterns.

Table 12.8: Specifications BF3C40

	Field of view	120°
	Depth of field	3~50 mm
	Distal end outer diameter	3.3 mm
	Insertion tube outer diameter	3.6 mm
	Working length	550 mm
	Channel inner diameter	1.2 mm
	Minimum visible distance	3 mm from distal end
Bending section	Angulation range	Up 180°, Down 130°
Total length		840 mm

6. OLYMPUS BF TYPE N20 (Table 12.9)

this is an ultra slim bronchoscope measuring only 1.8mm in diameter at the distal tip and 2.2 mm in diameter at the insertion tube. This bronchoscope is best suited for diagnosis of respiratory diseases in neonates and infants. It provides bright, sharp images due to high-resolution image guide fibres and distal end angulation of 160° up and 90° down supports accurate diagnosis.

Table 12.9: Specifications BFN20

	Field of view	75°
	Depth of field	2~50 mm
	Distal end outer diameter	1.8 mm
	Insertion tube outer diameter	2.2 mm
	Working length	550 mm
Bending Section	Angulation range	Up 160°, Down 90°
Total Length		840 mm

THE PHYSICS OF FLEXIBLE FIBEROPTIC ENDOSCOPES

A beam of light entering one end of an ordinary glass rod is trapped by repeated internal reflections off the walls until it emerges at the other end. It is this trapping of light within the glass rod that forms the basis for the use of fiberoptics to transmit images.

If a glass rod is heated and stretched, strands less than 25 microns diameter can be formed. These strands become flexible and are more properly termed fibers. The light entering such a fiber is trapped and, after many reflections off the walls (up to 10, 000 reflections/meter), emerges uniformly distributed over the exit face of the fiber. A specific or detailed image cannot be transmitted in a recognizable form over a single fiber, since the image is completely blurred on transmission down each fiber. Therefore, the image must be formed as a composite of many such fibers.

A large number of glass fibers fastened together with both ends tightly fixed makes a **Flexible bundle**. However, in order for an optical image to be transmitted through the bundle and subsequently identified, it is essential that the arrangement of fibers at each end of the bundle be precisely the same. This type of organized bundle is called a **Coherent bundle**. In such a bundle, complete optical insulation of each fiber in the bundle is essential. This is accomplished by coating each glass fiber with a 1 micron thick layer of another type of glass, which has a lower reflection index(RI) (a process called cladding). This helps maintain total internal reflection of light and aids in image transmission along the fiber, even though the fiber may be bent or twisted.

The resolution of an image formed by the composite of individual fibers in a coherent bundle is related to the diameter of the individual fibers. Resolution is improved by increasing the number of fibers in the bundle and using smaller diameter fibers. Glass fibers of 8 or less are not suitable for this purpose, as light is not transmitted well in such a narrow channel.

Light from the subject strikes the distal end of the bundle, is transmitted through the individual fibers in the bundle, and is reconstructed at the proximal end. The proximal image (at the eyepiece) consists of a lattice or raster of small spots of light, each with uniform intensity and color. This is similar to a television picture, which, in like manner, is composed of discrete picture elements or pixels. A typical fiberoptic image bundle has a diameter of 1.5 mm and contains about 10, 000 fibers of 10 to 12 microns in diameter. As a consequence, there are only 100 fibers or picture elements at any given diameter of the bundle, giving rise to the graininess seen in magnified endoscopy images. An objective lens is placed at the distal end of the image transmission bundle to focus the object being transmitted by the fibers. An eyepiece, consisting of several lenses, is placed in the handle to focus the proximal image from the bundle onto the viewer's retina and to provide image magnification. Except at the ends where fibers are fused for strength, the bundle is flexible. However, these fibers are delicate, and breakage may occur. When broken, a fiber will no longer pass its image, and the viewer will view a black dot in that fiber's location.

A fiberoptic bundle is also used to conduct light from an external source to the distal end of an endoscope. This light transmission bundle is subjected to fewer constraints, since no discernible image need be identified. Fiber size can be larger (typically 25 microns), and the fibers do not need to be arranged in a precise manner (**Incoherent bundle**).

The two remaining factors in endoscope design include controls to maneuver the tip and a means for providing a coordinated rotation. Small wires are used to bend the tip via a control lever, and the coordinated rotation is inherent in the basic construction. Coordinated rotation means that the tip rotates to the same degree as the handle when the latter is turned. Thus, the tip can be bent in any direction by a combination of rotation and bending.

BASIC ANATOMY OF A BRONCHOFIBERSCOPE

The basic structure of a bronchofiberscope is shown in Figure 12.7. The major components are

1. Handle
2. Insertion cord
3. Universal cord

Each of these is designed to contribute to the overall functioning of the endoscope and may come in several varieties, depending on the particular manufacturer and model. However, several basic generalizations exist across all instruments.

The Handle

This part is held by either the right or the left hand and contains the eyepiece for viewing, the lever or knob for controlling the bending motion of the tip, and access to the working (suction or injection) channel.

Most fiberscopes will have a tip locking lever to lock the bending tip at a desired position. This lock is used during bronchoscopic biopsy or photography and is not usually used during airway examination and intubation. Most handles are made to be held comfortably in one hand in such a way that the thumb can maneuver the bending lever and the index finger can regulate the suction. This allows the operator's other hand to be free to manipulate the insertion cord or endotracheal tube. The bending lever, which is located on the back of the handle, controls movement of the insertion cord tip in one plane of motion. Usually, the connection of the handle to the insertion cord is tapered, such that an endotracheal tube may be held there by being pushed onto the taper. The eyepiece contains a diopter adjustment ring to focus and adjust the eyepiece to fit each viewer's eye.

Insertion Cord

That portion of the fiberscope that is inserted into the patient and over which endotracheal tubes are passed during fiberoptic intubation is called the insertion cord or tube. It contains the light guide and image transmission bundles, the working channel, and the tip bending control wires. These are wrapped with a water-impermeable coating the outside diameter of which determines the size of the smallest endotracheal tube that can be used. The insertion cord is flexible (Fig. 12.8). The only portion of the insertion cord that is designed for maximum bending is the distal tip. This tip is made more flexible by enclosing the contents within a series of metal rings, which are joined by hinges to metal wires along two sides. The tip is then able to bend up and down at right angles to these hinges according to the tension in two control wires. The coating on the tip

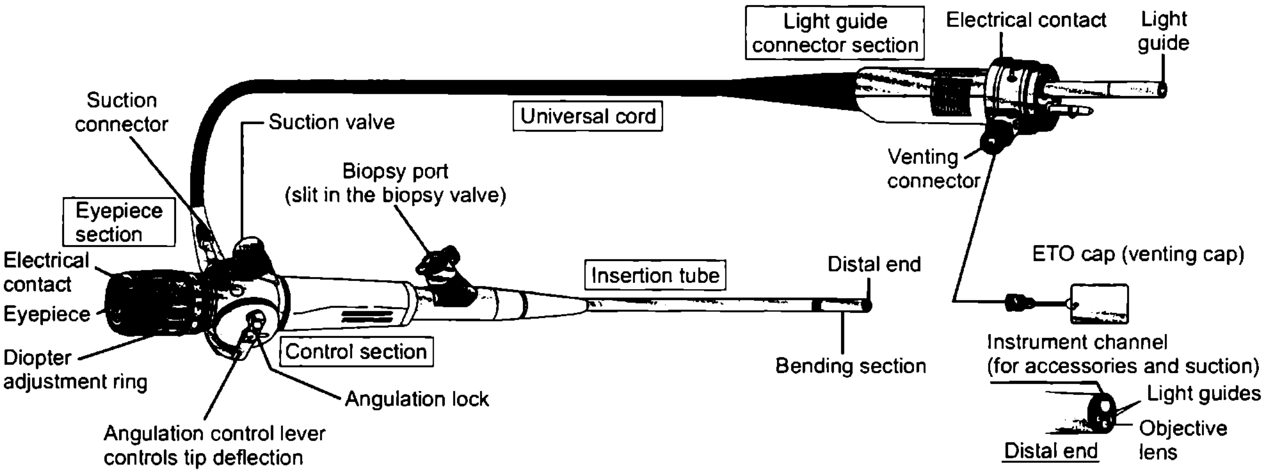

Light guide connector section
Electrical contact
Light guide
Suction connector
Suction valve
Universal cord
Venting connector
Biopsy port (slit in the biopsy valve)
Eyepiece section
Electrical contact
Eyepiece
Insertion tube
Distal end
ETO cap (venting cap)
Diopter adjustment ring
Control section
Bending section
Instrument channel (for accessories and suction)
Light guides
Angulation lock
Objective lens
Distal end
Angulation control lever controls tip deflection

Fig. 12.7: Basic anatomy of bronchoscope

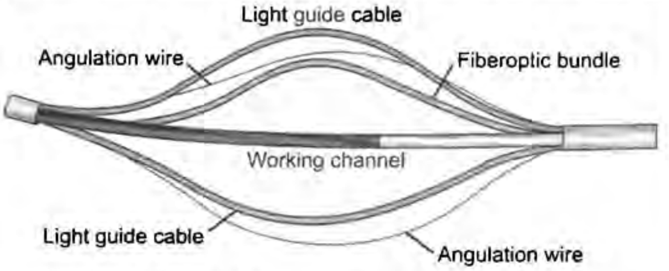


Fig. 12.8: Insertion cord anatomy

is made of thin rubber, so that it remains sealed yet flexible. The delicate nature of the rings, wires, bundles, and coating makes this a very easily damaged region.

Light Guide Bundles

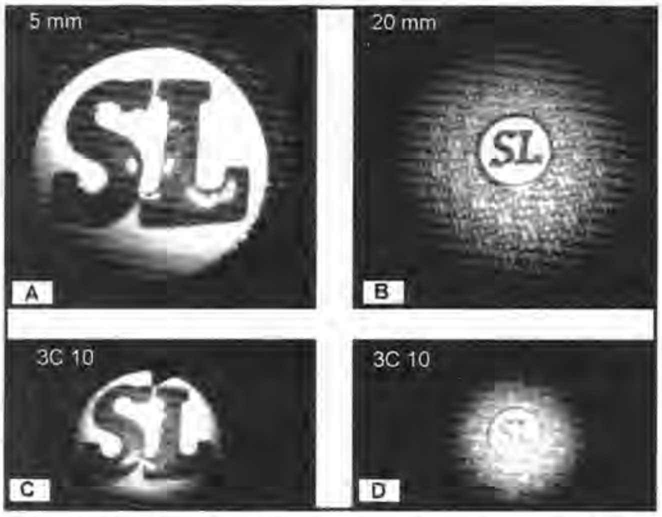
The light is transmitted through one or two light guide bundles to the tip of the fiberscope. These glass fibers extend to the light guide bundle of the universal cord, which is connected to the external light source.

Image Transmission Bundle

The basic optical construction of the viewing portion of the fiberscope involves the objective lens, image transmission bundle, and eyepiece. Since the distal tip is sealed to eliminate patient secretions and cleaning solutions, focusing by movement of the objective lens is not possible. Thus, the fiberscope is "fixed focus" at the distal tip. Light reflected off the object is focused by the objective lens onto the distal end of the image transmission bundle (object face). This image is then transmitted to the proximal end of the image transmission bundle to the face near the eyepiece (image face). Because the glass fibers in the image transmission bundle are placed so that each fiber is in the same relative location on the image face as the object face, the image seen will faith fully represent that object.

The depth of view field is the range of distances from the tip of the fiberscope within which objects can be located and appear with the same degree of clarity to the viewer. The exact range depends on the fiber size and the effective aperture of the objective lens; however, most fiberscopes have a depth of view field of 3 to 50 mm.

The field of view is the cone-shaped visual field [in degrees (°)] afforded by the design of a particular fiberscope (Fig. 12.9). The field of view of the fiberscope is governed by the number of fibers and the amount of field allocated to each fiber. A wider field of view can be accomplished by increasing the number of fibers while maintaining detail, or by sacrificing detail with a smaller number of fibers and allocating more visual field per fiber. Most endoscopes have a field of view of 55 to 100 degrees.



Figs 12.9A to D: Field of view–A to D. Endoscopic view of letters from 5 and 20 mm distance as seen through two different fiberscopes: (A, B) Olympus C10 adult bronchofiberscope and (C, D) olympus 3C10 pediatric bronchofiberscope

The upper limit of magnification is practically limited by the illumination of the field as well as the design and construction of the small optical system, which must be enclosed at the tip of the fiberscope.

Working Channel

This channel extends from the handle of the fiberscope to the tip of the insertion cord and can be used to suction secretions, inject drugs, insufflate oxygen, or pass various biopsy and brush instruments. For adequate suctioning of secretions, it is recommended that a working channel be at least 2 mm in diameter.

Tip Bending Lever

The bending of the distal section of the insertion tube is achieved by movement of the bending lever located at the handle. Two separate small wires travel from the bending lever to the tip of the fiberscope. When the lever is moved downward, the wire that controls the anterior deflection of the tip is tightened, and the tip of the fiberscope bends upward or anteriorly. When the lever is moved upward, the tip of the fiberscope bends downward or posteriorly. Care should be exercised not to put excessive pressure on the lever when the tip of the fiberscope is against resistance. This will result in break age of the delicate wire, with loss of bending control. With substantial usage, and especially with improper handling, loss of distal tip flexion is common.

Distal Tip

All fiberscopes are "frontal view" instruments, i.e., the objective lens is perpendicular to the longitudinal axis of the instrument.

Universal Cord

The universal cord contains the light guide fiber bundle and electrical wiring for the automatic photography exposure system. The universal cord ends at the light guide connector. The light guide connector contains the plug, air vent connector, and electrical contacts and is plugged into the light source prior to use of the fiberscope. The ETO(ethylene oxide) cap must be installed for ETO gas sterilization and aeration, and in the event of transportation, it must be removed prior to immersion of the fiberscope into water or disinfectant solutions, or when the fiberscope is in use.

COMPARISON OF AVAILABLE FIBERSCOPES

Several excellent fiberscopes are currently available. These fiberscopes can be used for a variety of purposes, from upper airway examination and intubation of the trachea to diagnostic and therapeutic bronchoscopy. These fiberscopes can be characterized by several important design criteria that are useful for comparison.

Diameter of Insertion Cord

The diameter of the insertion cord determines the size of the endotracheal tube or airway with which the fiberscope can be used. The inside diameter of the endotracheal tube should generally be 1 mm larger than the diameter of the insertion cord. Thus, a fiberscope of small diameter will be necessary for pediatric applications or for use in a double-lumen tube.

A small fiber-scope, however, has several disadvantages when it is used with larger tubes. These include reduced working channel size, small objective image, excessive flexibility (reducing its effectiveness as a "stylette"), and increased susceptibility to damage. Stiffer insertion cords will partially overcome the greater flexibility of the small fiber-scopes; however, this stiffness obviously reduces the flexibility that is helpful during airway endoscopy and bronchoscopy.

Length of Insertion Cord

The length of the insertion cord defines the usable length of the fiberscope.

The Size of the Working Channel

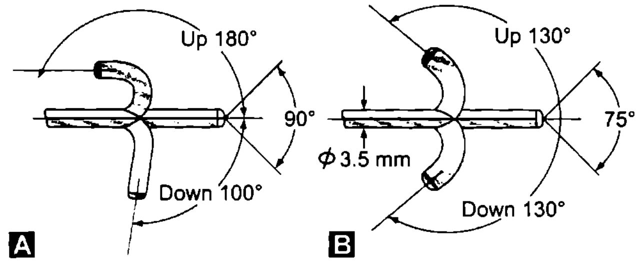
The presence and size of the working channel should be considered. Secretions and blood obscuring the view is a major cause of failure during fiberoptic intubation. The working channel can be used to suction these secretions during viewing and to assist exposure of the epiglottis and vocal cords. Small channels are inefficient for suctioning, can easily be clogged with secretions, and must be meticulously cleaned each time they are used. Since the channel increases insertion cord diameter, some small-diameter fiberscopes have eliminated the channel to achieve a smaller overall diameter.

The Field of View

The field-of-view angle defines the overall picture available to the viewer. A wide field of view will give a good perspective on the anatomy; however, this may sacrifice the resolution or image quality. Fortunately, most of the presently available fiberscopes combine a wide depth of field coupled with a reasonable field of view and image resolution. These qualities, as well as the durability and arrangement of the handle controls, are best evaluated individually.

The Bending Radius of the Distal Tip

The bending characteristics of the distal tip of the insertion cord should be evaluated. Sufficient bending must be available to allow maneuvering in the airway, especially in the presence of pathology or a compromised airway. In general, for intubation of the trachea, the upward flexibility is most important, since the most difficult angle of the airway



Figs 12.10A and B: Bending section of two fiberscopes with different degrees of up and down bending capability and different degrees of depth of field of view

is usually the upward bend from the posterior pharynx behind the epiglottis into the trachea. However, for evaluation of the bronchial tree and management of the airway in the presence of mass or tumor, both upward and downward bends become critical. Upward bending of 160° or more and down ward bending of 120 or more are needed for successful airway management under different circumstances (Fig. 12.10).

The Control Mechanisms of the Bending Tip

The control mechanism of the bending section of the insertion cord is important. The thumb control lever system, which is placed on the back section of the body of the fiberscope, is considered superior by many operators. The maneuverability of the instrument is greatly improved, and the fiberscope can be handled by either the left or right hand without difficulty. Other factors that should also be considered when purchasing a fiberscope are the need for taking pictures, the use of video systems, and the compatibility with existing fiberscopes and light sources. Extremely important are the quality and speed of service provided by the manufacturer. Even with careful handling, fiberscopes will eventually need repair and servicing. A convenient service provided by the company is the loan of an instrument while repairs are being conducted.

ACCESSORY INSTRUMENTS

A variety of accessories and attachments are available for the fiberscope. Some of these accessories are an integral part of the fiberscope necessary for viewing, cleaning, or testing. Most of the remaining attachments are used either for teaching or for photography.

Light Sources

The ability to distinguish the object depends on adequate illumination; thus, the light source is an integral part of the fiberoptic endoscope system. Various light sources are available, which provide adequate illumination not only for viewing but also for taking pictures or videotapes. An intense light is generated and is focused on the proximal end of the light guide cable by a source lens or a spherical reflecting mirror. A heat filter or reflecting mirror is used to reduce the amount of heat focused on the light guide cable. The powerful light source needed for videotaping is more expensive, but it will provide adequate light for viewing when the fiberscope has sustained damage and part of the light-carrying fibers are broken.

Teaching Attachments

Teaching attachments are available that allow second viewer to observe as the endoscopist carrie out the procedure. They are attached to the eyepiec of the fiberscope and provide an invaluable teachin aid. The teaching attachment allows splitting of th beam, so that an observer has the same view as th endoscopist.

Forceps and Brushes

A variety of forceps for tissue biopsy and remov of foreign bodies, and different size brushes ar available. Anesthesiologists are rarely faced wit situations requiring accessories other than th cleaning brush.

CLEANING AND STERILIZATION

After each use, the fiberscope should be cleaned ar disinfected to prevent damage to the fiberscope dried secretions and transmission of disease. Speci recommendations for sterilization or disinfecti made by the manufacturer and by each health ca facility should be followed. As a general rule, t insertion cord of all fiberscopes is immersib However, the handle and the universal cord of so instruments may be damaged by immersion solutions, although most modern fiberscopes are designed to withstand complete immersion in disinfected solutions.

The fiberscope should be washed immediately after use, and the working channel should be flushed with water to remove secretions before they dry. Prior to soaking in disinfecting solution, all portions of the fiberscope to be immersed should be inspected for defects that might allow liquids to enter into the sealed portions. The rubber covering of the distal portion of the insertion cord should be carefully examined, as frequent use of the fiberscope may cause tears and defects in this covering. Totally immersible fiberscopes should be tested for leaks using a leakage tester and pressurized air prior to immersion in the solution. Since solutions will cause extensive damage to the optical system, the fiberscope should promptly be sent to the manufacturer for appropriate repair when defects are identified.

After inspection, the suction port assembly should be removed, and the immersible portions of the fiberscope should be soaked in disinfectant solution. Solutions recommended vary with individual manufacturers and include 0.5% povidine-iodine; 2% glutaraldehyde; mild, non-abrasive soap solutions; and 0.016% iodophor. Recommended immersion times after use in non-infected patients vary from 10 min for glutaraldehyde, to 20 min for the iodine-containing solutions, to 30 min for the soap solutions. Each solution is potentially caustic to the materials in the fiberscope, and, thus, the manufacturers' recommendations for disinfectant concentration and maximum soaking time should be carefully observed.

The working channel should be filled with disinfectant solution using a syringe. The use of a cleaning brush may be needed for removal of secretions from the working channel. The brush should only be inserted at the handle end to avoid kinking of the brush in the fiberscope and subsequent difficulty removing it. Finally, the fiberscope should be washed and the working channel suctioned with water to remove all traces of the disinfectant solution. The portions of the fiberscope that cannot be immersed are wiped with a cloth containing 70% alcohol; however, the contact time with the alcohol should be limited, as it can destroy the rubber coating on the fiberscope.

If the patient has tuberculosis or other transmissible illness, the entire fiberscope should be sterilized. Fiberscope sterilization is also important prior to use on patients with immune deficiencies. Complete sterilization of the fiberscope can be accomplished by ethylene oxide gas sterilization.

Manufacturers recommendations should be followed, so that damage does not occur. The ethylene oxide cap must be securely attached to the venting connector on the light guide connector and must remain in place throughout the sterilization and aeration process. This is necessary to avoid pressure buildup inside the fiberscope during gas sterilization. This cap must be removed prior to immersion and clinical examination. It is important to recognize that the gas sterilization procedure is lengthy, and it may take as long as 24 hour before the fiberscope is ready for use.

After cleaning, the fiberscope should be dried thoroughly and stored for subsequent use. The ideal container allows the insertion cord to remain straight. Carrying cases or small sterilization trays, in which the insertion cord is bent, are less desirable for storage, as the bending stresses the insertion cord and will ultimately damage fibers. The storage location must be clean, dry, well-ventilated, and maintained at room temperature. Direct sunlight, high temperature, high humidity, and X-ray exposure may cause fiberscope damage.

THE FIBEROPTIC CART

The immediate availability of a fiberscope, light source, ancillary equipment and routinely used supplies is critical for effective application of the fiberscope in airway management. A properly equipped fiberoptic cart with large wheels is ideal. The cart should have a minimum of three shelves or drawers. The cart can be moved to the operating room or to the bedside at short notice to allow convenient access to all the accessories used for airway endoscopy and intubation (See Fig.12.6).

SUGGESTIONS FOR FIBERSCOPE USAGE

A variety of do's and don'ts have been suggested to improve the usage, avoid the complications, and increase the life expectancy of the flexible fiberscope. The following is an expanded list of do's and don'ts, which, if carefully applied, will avoid unnecessary and untimely instrument damage.

Do's

1. Do clean, prepare, and check all the necessary equipment and supplies before each use to be certain they function satisfactorily.
2. Do adjust the brightness of the light to a comfort able but minimum effective level to avoid thermal mucosal injury as well as to protect the user's eye.
3. Do lubricate the insertion cord with a sterile water- soluble lubricant.
4. Do adjust the tip of insertion cord to the neutral position before insertion into the endotracheal tube and before withdrawal from the tube.
5. Do advance the fiberscope gently and small distances at a time.
6. Do operate the tip bending lever gently.
7. Do clean the fiberscope and the suction channel immediately after each use.
8. Do dry the fiberscope thoroughly, including all lenses and electrical contacts, prior to storing.
9. Do store the fiberscope with the insertion cord as straight as possible.
10. Do use the correct light source adapter to prevent damage to the universal cord fibers.
11. Do follow hospital and manufacturers' recommendations for cleaning and disinfecting.

Don'ts

1. Do not drop the fiberscope, as it may break and be extensively damaged.
2. Do not sharply bend the insertion cord, as this will break the delicate glass fibers.
3. Do not strike the distal end of the insertion cord on a hard surface, as this may crack the objective lens.
4. Do not squeeze, bend, or twist the distal bending section by hand, as this will damage the bending mechanism.
5. Do not leave the fiberscope plugged into the light source with the lamp on when not in use. This will increase the risk of thermal injury and will reduce the life of the light bulb.
6. Do not scratch the electrical contacts with sharp tools. This will cause damage and improper contact.
7. Do not spill liquids on the head of the fiberscope (non-immersible), light source, or photographic and videotaping systems in order to prevent equipment damage and electrical hazards.
8. Do not use abrasive cleaners on lens surfaces in order to prevent scratches.
9. Do not withdraw the fiberscope with the angle lock lever in the "engaged" position or while the distal tip is bent. This will cause extensive damage to the bending section and bending control wires and may cause trauma to the airway.
10. Do not twist the fiberscope with force when the tip is in a narrow orifice or tube. This will damage the insertion cord and may cause tissue damage.
11. Do not apply force when bending the tip of the fiberscope, in order to prevent rupture of the bending wires and loss of bending of the tip.
12. Do not expose the fiberscope to direct sunlight, dust, high humidity, and high temperature in order to prevent instrument damage.
13. Do not store the fiberscope in the carrying case. It is airtight and may predispose to organism growth and contamination.
14. Do not expose the fiberscope to excessive X-ray radiation. This will result in a yellow discoloration and darkening of the glass fibers.
15. Do not try to introduce the fiberscope with force in any case.
16. Do not immerse a fiberscope with a venting cap on, or gas sterilize a fiberscope without a venting cap on, if the fiberscope has such a cap.
17. Do not exceed 10 hr of immersion for cold sterilization.

Anatomy for the Bronchoscopist

Once the bronchoscope is introduced with the patient in the supine position, and the bronchoscopist at the head end of the patient, the palate will appear at the top, and the posterior pharyngeal wall and the adenoids at the bottom. Beyond the edge of the soft palate, the larynx, esophagus, and the base of the tongue are visualized. Dynamics of movements of the larynx are assessed by placing the bronchoscope just above the larynx and movements are evaluated as the child is made to wake up from general anesthesia. When performed under local anesthesia, these are usually observed before traversing the vocal cords. There are considerable differences between the infant and the adult larynx. The infant larynx is placed more anteriorly in the neck compared to the adult, and it often appears to stand up on a pedestal from the floor of the pharynx. The epiglottis has a much more pronounced curvature (omega or U shaped) compared to the adult epiglottis and the arytenoid cartilages may be very prominent in the infant (Fig. 12.11).

In contrast to the adult, the cuneiform and corniculate cartilages may not be discernible as separate structures in the child. The sub glottic space is the narrow portion of the airway in infants and young children as compared to the glottis in the adults. Hence, the selection of bronchoscope for infants and young children should take into consideration that the area beneath the vocal cords is the area of limitation, not the space between the vocal cords as in adults (Fig. 12.12).

The trachea is entered after passing the cricoid cartilage. In children the trachea is nearly round, with the cartilages extending visibly through an arc of approximately 320 degrees (Fig. 12.13). It is normal to see some inward protrusion of the membranous portion of the airways (trachea and main bronchi) on coughing. The main carina is keel shaped and oriented in an anteroposterior plain. In the adult the main carina is sharp and a widened carina in adults may indicate subcarinal lymphadenopathy. In the child the main carina is often quite blunted. The right mainstem bronchus is immediately seen on peering down the trachea. The left main bronchus can be visualized in its entirety from the carina, after turning towards the left, and even then it takes a curving course so that its bifurcation cannot be seen from the carina. The shape of the main stem bronchi is very similar to that of the trachea, with a prominent posterior membranous portion.Various parts of tracheobronchial tree are shown in plates.

The right upper lobe division takes off just beyond the carina at an angle of approximately 100 degrees (Fig. 12.14). The right upper lobe bronchus itself may have a length of 1cm before dividing into the anterior, posterior and apical segmental bronchi. Beyond the origin of the right upper lobe bronchus, the right main stem bronchus continues as the bronchus intermedius. This bronchus may extend for 2-2.5 cm at which point it gives rise to the middle lobe bronchus anteriorly, the superior segment of the right lower lobe posteriorly and the right lower lobe bronchus that divides into basilar segments.

The left mainstem bronchus is 4-4.5 cm in length and terminates into the upper lobe and lower lobe bronchi. As the left upper lobe bronchus ascends superiorly, the lingular bronchus arises and extends slightly down-ward in an inferior-lateral direction (Fig. 12.15).

The upper division bronchus of the upper lobe passes beyond the orifice of the lingula and gives rise to the apicoposterior and the anterior segments. Immediately on entering the left lower lobe bronchus arises the superior segment of the left lower lobe and that descends posteriorly. The left lower lobe bronchus beyond the origin of the superior segment is usually 1 cm in length before giving rise to the basal bronchi. Figures 12.16 to 12.19 show the various branches of the bronchial tree using the standard nomenclature.

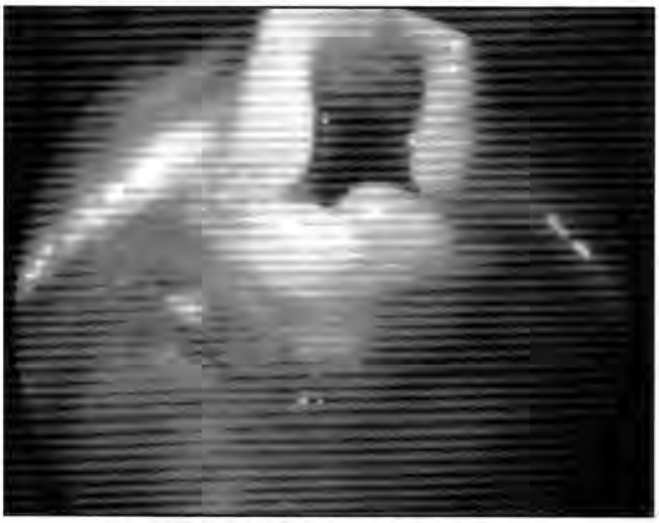


Fig. 12.11: Bronchoscopic view of larynx
(For color version see Plate 4)

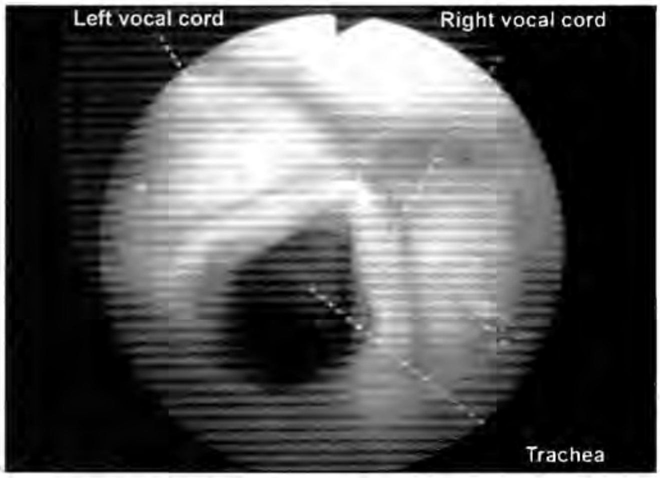


Fig.12.12: Bronchoscopic view of vocal cords
(For color version see Plate 4)

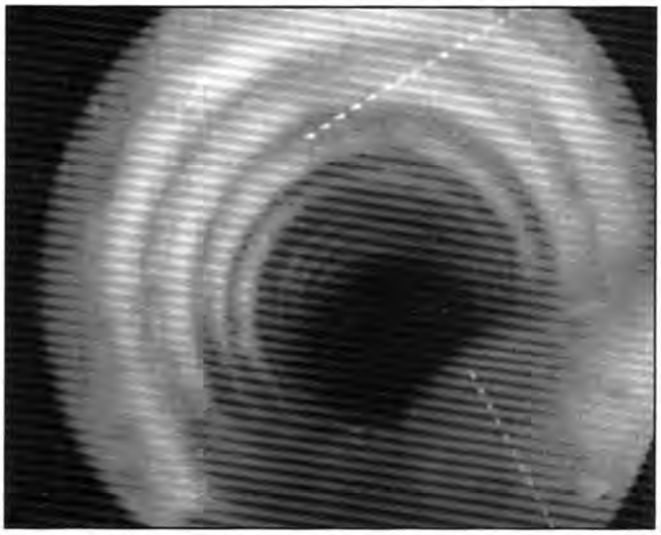


Fig. 12.13: Tracheal rings *(For color version see Plate 5)*

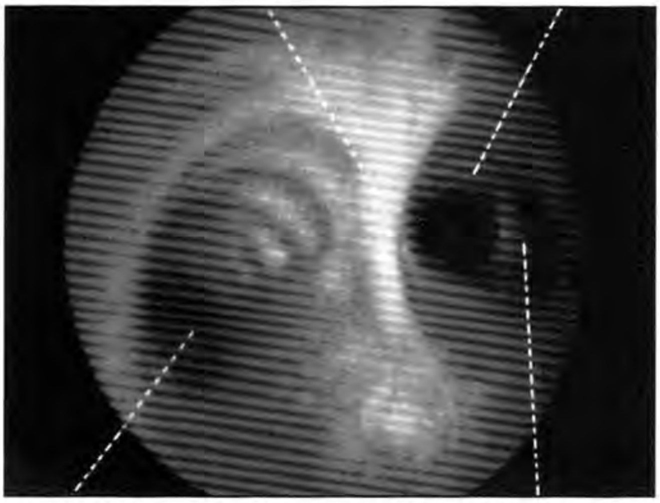


Fig. 12.14: Right mainstem bronchus with right upper lobe take off *(For color version see Plate 5)*

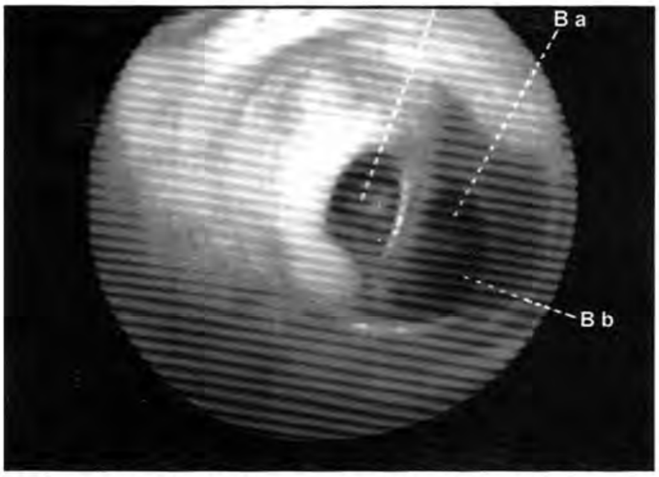


Fig. 12.15: Left bronchus *(For color version see Plate 5)*

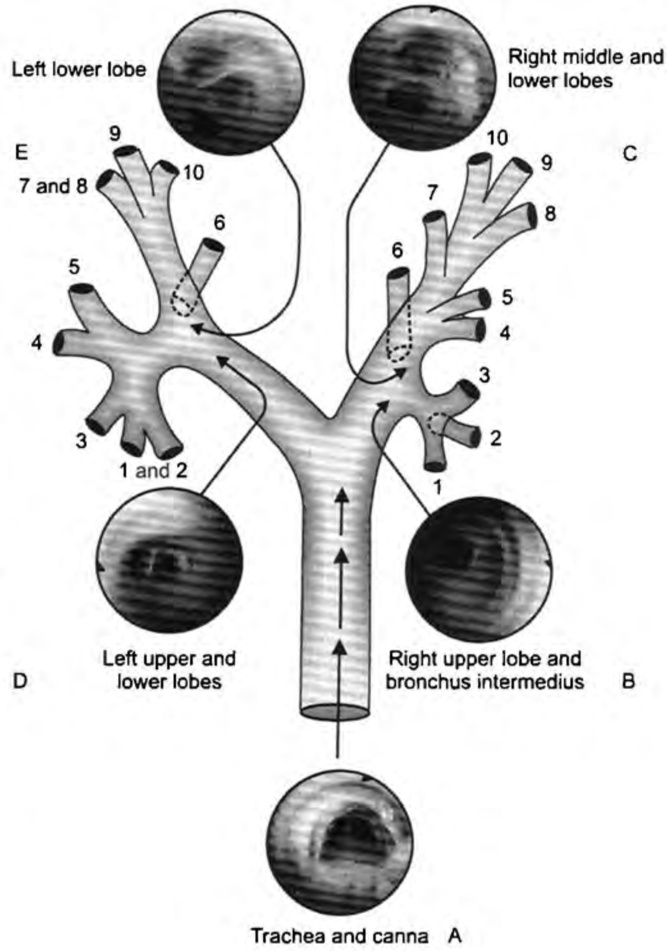

Left lower lobe
Right middle and lower lobes
E
9
7 and 8
10
6
5
4
3
1 and 2
10
9
C
7
8
6
5
4
3
2
1
D
Left upper and lower lobes
Right upper lobe and bronchus intermedius
B
Trachea and canna A

Fig. 12.16: Bronchial anatomy

Bronchoscopic report should use standard terminology regarding the anatomical segments and lesions if any should be clearly drawn and demarcated, with hard copies of still photographs or a video recording.

Preparation of the Patient: The preparation of the procedure starts with preparing the patient mentally for the procedure and explaining the procedure in detail to the child and parents and taking an informed consent for the procedure. This minimizes the amount of sedation that would otherwise be required in an uncooperative child. The patient must be adequately prepared for the procedure. In the pediatric intensive care unit(PICU), the patient who is being mechanically ventilated, informed consent must be obtained from the parents after explaining the risks and benefits of the procedure.

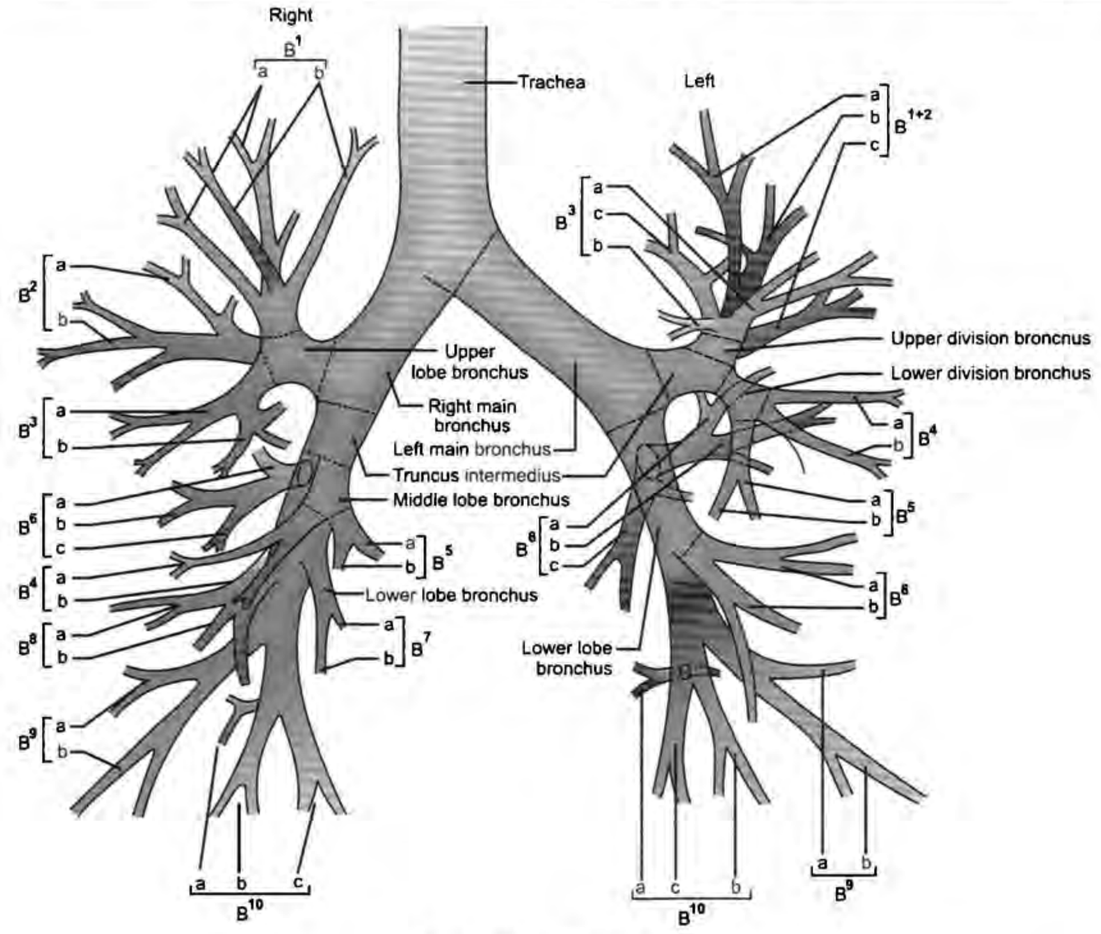

Right
B^{1}
a
b
Trachea
Left
a
b
c
B^{1+2}
a
c
b
B^{3}
a
b
B^{2}
Upper lobe bronchus
Upper division broncnus
Lower division bronchus
a
b
B^{3}
Right main bronchus
Left main bronchus
a
b
B^{4}
Truncus intermedius
a
b
c
B^{6}
Middle lobe bronchus
a
b
B^{5}
a
b
B^{5}
a
b
c
B^{6}
a
b
B^{4}
Lower lobe bronchus
a
b
B^{8}
a
b
B^{8}
a
b
B^{7}
Lower lobe bronchus
a
b
B^{9}
a
b
c
B^{10}
a
c
b
B^{10}
a
b
B^{9}

Fig. 12.17: Bronchial tree

Oxygen supplementation during the procedure is mandatory in young infants and children especially those with poor respiratory status. Supplemental oxygen can be delivered with a nasopharyngeal prong through one nostril with the bronchoscope passed down the other or by a facemask over the nose and mouth.

Before the procedure the nose and pharynx must be suctioned after the patient has been sedated and the upper airway anesthetized. A naso gastric tube should be gently passed into the stomach and any contents should be emptied. The patient should be placed supine on the procedure table and gently restrained by an assistant. In younger children, it is helpful to swaddle the arms in a sheet, leaving the chest free for observation and auscultation. ECG electrodes are than attached to monitor heart rate and rhythm. A pulse oximeter to monitor the oxygen saturation should be used. The assistant should gently hold the head and the shoulders, while reassuring the child gently.

Sedation Analgesia and Monitoring During Bronchoscopy

As a basic requirement all resuscitative equipment including oxygen, mask, ambu bag laryngoscope, endotracheal tubes, suction equipment, suction catheters and drugs including atropine, salbutamol and adrenaline must be available.

In addition pulse oximeter and cardiac monitor should be available. At least one skilled assistant to monitor sedation level, vital signs and oxygen saturations is mandatory. Desaturation and bradycardic episodes should be monitored and promptly treated by first removing the bronchoscope out of the airway and giving oxygen until the patient recovers from such an episode. Each pass into the

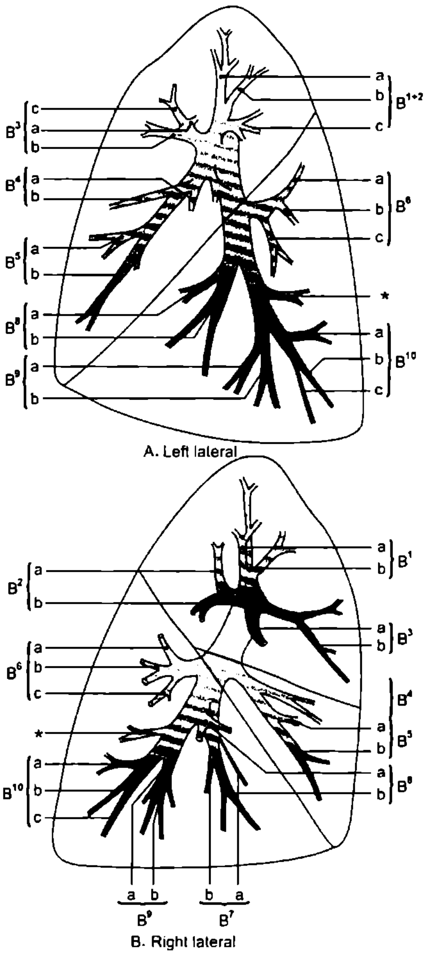


Fig. 12.18: Nomenclature of segments(Japan,1950)

airway tree should not be more than 15-20 seconds specially in hypoxemic ventilated patients in the PICU.

Six hours with nothing by mouth is required for all infants and children before bronchoscopy. An intravenous catheter is secured, and consent is obtained from each patient/parent. The consent form delineates potential risks and complications balanced against targeted objectives and benefits.

Local Anesthesia

This is recommended in addition in patients receiving intravenous sedation to prevent airway reflexes causing minimal cough, bronchospasm or bradycardia.

The nasopharynx, usually the right side, is topically anesthetized by applying 0.3-2.5 ml of 2 percent lidocaine solution, not exceeding 8 mg/kg (to avoid risk of seizures), followed by local lubrication with lidocaine jelly.

With the exception of tracheostomy evaluation or endotracheal introduction in ventilated children, proce dure is performed transnasally. Its important to keep in mind that as the vocal cords are approached, local anesthetic solution is sprayed to anesthetize the vocal cords. This usually results in smooth passage of the bronchoscope without causing the reflex bronchospasm. Laryngospasm may occur but is usually self resolving. Oxygen may be given throughout the procedure by blowing in front of the face or by keeping the nasal cannulae to prevent hypoxemia.Transtracheal or cricothyroid instillation of local anesthetic solution is usually reserved for older children or adults, to anesthetize the distal tracheal mucosa.

Sedation and General Anesthesia

Presedation assessment

Adequate presedation assessment regarding history of fever or upper respiratory infection, asthma, allergies, significant past history, nil by mouth status, airway assessment and general physical condition is important and should be documented.

Sedation

Intravenous sedation allows the patient to remai reasonably comfortable while ventilation an oxygenation remain adequate. 0.1 mg/kg intra venous midazolam to a maximum of 2.5 mg per dose may be given slowly over 2 minutes. Ketamine 1-2 mg/kg, or propofol are used if the abov modalities fail to achieve appropriate sedation fo the procedure. All procedures requiring intravenou sedation are performed in the pediatric intensiv care unit (PICU) or the operation theater. Whe general anesthesia is provided, the flexible fiberopti bronchoscope is introduced via a customized adapte through an appropriate endotracheal tube or laryngeal mask airway (LMA). In some cente medications commonly used for sedation ar fentanyl 1-3 mcg/kg/h and midazolam 0.1 mg/k Reversal agents (naloxone and flumazenil) may b used in the post-operative period.

One of the protocols for flexible fiberopt bronchoscopy (FFB) in the PICU includes one of t

Bronchial nomenclature

Right lung			Left lung			
Upper lobe	B^{1} : R. apicalis	a. Rm. apicalis proprius b. Rm. (subapicalis) ventralis	Upper lobe	Upper division bronchus	B^{1+2} : R. apicodorsalis	a. Rm. apicalis b. Rm. (subapicalis) dorsalis c. Rm. (lobi sup. ventr.) horizontalis
	B^{2} : R. (lobi superioris) dorsalis	a. Rm. (subapicalis) dorsalis b. Rm. (lobi sup.) horizonatalis				
	B^{3} : R. (lobi superioris) ventralis	a. Rm. (lobi sup. ventr.) lateralis b. Rm. (lobi sup. ventr.) medialis			B^{3} : R. (lobi superioris) ventralis	a. Rm. (lobi sup. ventr.) lateralis b. Rm. (lobi sup. ventr.) medialis c. Rm. (lobi sup. ventr.) superior
Middle lobe	B^{4} : R. medius lateralis	a. Rm. lateralis b. Rm. medialis		Lower division bronchus	B^{4} : R. lingualis superior	a. Rm. lateralis ventralis b. Rm. (lobi sup.) ventralis
	B^{5} : R. medius medialis	a. Rm. lateralis b. Rm. medialis			B^{5} : R. lingualis inferior	a. Rm. superior b. Rm. inferior
Lower lobe	B^{6} : R. (lobi inferioris) superior	a. Rm. superior b. Rm. lateralis c. Rm. medialis	Lower lobe		B^{6} : R. (lobi inferioris) superior	a. Rm. superior b. Rm. lateralis c. Rm. medialis
	B : R. (lobi inferioris) subsuperior				B : R. (lobi inferioris) subsuperior superior	
	B^{7} : R. mediobasalis	a. Rm. dorsalis b. Rm. ventralis				
	B^{8} : R. ventrobasalis	a. Rm. lateralis b. Rm. basalis			B^{8} : R. ventrobasalis	a. Rm. lateralis b. Rm. basalis
	B^{9} : R. laterobasalis	a. Rm. lateralis b. Rm. basalis			B^{9} : R. laterobasalis	a. Rm. lateralis b. Rm. basalis
	B^{10} : R. dorsobasalis	a. Rm. dorsalis b. Rm. lateralis c. Rm. medialis			B^{10} : R. dorsalis	a. Rm. dorsalis b. Rm. lateralis c. Rm. medialis

Fig. 12.19: Bronchial nomenclature(Chest, 1943)

following. propofol, 2.5 mg/kg loading dose, and subsequent boluses of 0.5 to 1 mg/kg; (2) ketamine, 1 to 2 mg/kg loading dose, following atropine, 0.02 mg/kg, and midazolam, 0.1 to 0.2 mg/kg; or (3) supplementation of morphine and midazolam boluses in patients receiving mechanical ventilation who were already receiving continuous infusions of these drugs.

With close monitoring of heart rate, respiratory rate and pulse oximetry, most intravenous sedatives can be safely given for FFB in neonates and children. Post procedural monitoring for stridor, bronchospasm, distress or desaturation as well as nausea and vomiting is important. Use of oxygen, nebulization and intravenous steroids may be required if necessary.

Position

For Nasal Insertion: If a nasal insertion is planned bronchoscopy can be performed with the patient lying supine, semirecumbent, sitting facing the bronchoscope or in a lateral decubitus position with the bronchoscopist standing at the head end of the patient. The lateral decubitus position can make the procedure difficult at times. In older patients and adults, some bronchoscopists prefer to perform the procedure with the patient sitting erect and standing facing the patient. But this position is not preferred by bronchoscopists in younger children. Performing the procedure in ventilated patients makes it difficult to stand at the head end. This can be achieved in smaller children by rotating them 90° so the head is at the edge of the bed. A totally supine position is the most comfortable for most patients.

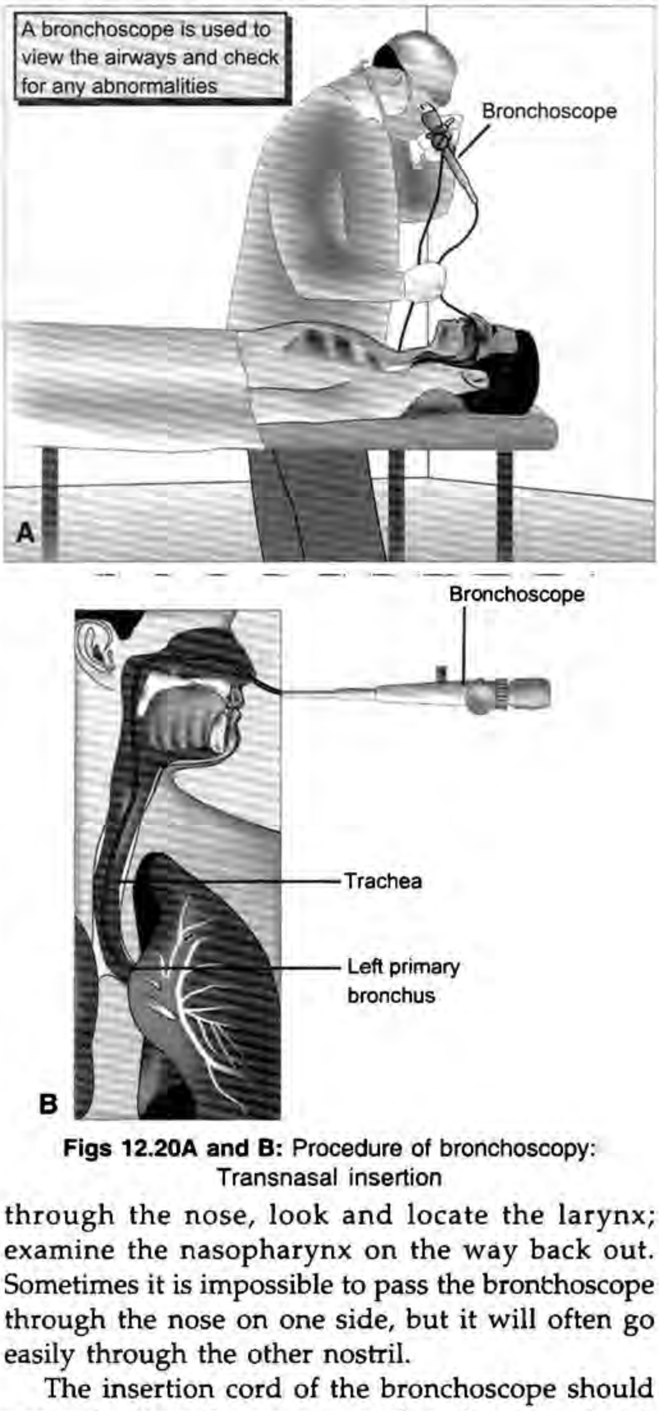
For Oral Insertion: The bronchoscopist can be in front of the patient if he is sitting or stand at the head end of the patient if he is supine. Any change of position of the bronchoscopist also changes the spatial orientation of the tracheobronchial anatomy.

Location: Although the procedure can be performed anywhere in the hospital, it is preferable to perform routine procedure in the central facility or the bronchoscopy room where there are adequate facilities for monitoring and resuscitation of the patient. Assistants should be adequately trained and experienced. Two assistants are usually required the technician and a trained nurse. Anything, which might be needed, will be readily available and this increases the safety of the patients.In sicker children, specially with respiratory distress or oxygen requirement, bronchoscopy should be performed in the pediatric intensive care unit.

Following is the technique is currently practiced and recommended by the authors. This technique has been originally described by Dr Robert wood in his training course.

Insertion of the Bronchoscope

Transnasal insertion (Figs 12.20A and B, 12.21): Transnasal insertion is the most common, convenient and informative method. It allows complete examination of the upper and the lower airways. After anesthetizing and suctioning the nose, insert the tip of the bronchoscope into the larger of the two nostrils. Before inserting position the tip of the bronchoscope just outside the nostril with the hand braced against the patient's cheeks with the last two fingers of the left hand and then look through the bronchoscope before advancing the instrument into the nose. Advance the bronchoscope slowly along the floor of the nose, guiding it under direct vision through the largest passageway you can find. In children this will be the middle meatus, between the inferior and middle turbinates. If you see a triangular passageway, you will most likely be taking the path of least resistance. If you feel resistance, use visual guidance to direct the tip of the scope to advance ahead. Do not aim the bronchoscope up towards the glabella; if you see light illuminating the nose you are going in the wrong direction. Pass the bronchoscope through the nose the same way as you would pass a nasogastric tube. When it is through the nose, look and locate the larynx; examine the nasopharynx on the way back out. Sometimes it is impossible to pass the bronchoscope through the nose on one side, but it will often go easily through the other nostril.


A bronchoscope is used to view the airways and check for any abnormalities
Bronchoscope
A
Bronchoscope
Trachea
Left primary bronchus
B

Figs 12.20A and B: Procedure of bronchoscopy: Transnasal insertion

The insertion cord of the bronchoscope should protrude from the nose in such a direction that it does not push or pull on the nares. There is a tendency for all bronchoscopists to pull the tip of the nose upwards with the insertion cord of the scope; this makes the patient very uncomfortable. Hold the scope so that the insertion cord extends out from the nose and then passes slightly down towards the mouth.

The nasal passage is often tight in patients of all ages. Virtually all patients feel some sensation, regardless of the amount or type of local anesthesia. If the patient has been properly prepared to feel pressure rather than pain, he will most probably remain comfortable. The advancing tip is usually directed caudad. On reaching the nasopharynx the tip should be deflected further caudally and advanced until the base of the tongue and epiglottis is identified. Once the tip of the bronchoscope enters the posterior pharynx, most patients no longer feel much sensation at all. Occasionally, however, it is helpful to put more topical anesthetic in the nose. As you closer to the choanus spray another small amount of topical anesthetic on the posterior wall. It is against this wall that the insertion cord of the bronchoscope will push as it is advanced it into the lung. Effective anesthesia along the posterior pharyngeal wall will help ensure a smooth, comfortable passage. To achieve good control keep the insertion cord of the scope as straight as possible. The major advantage of this route is that one can avoid the tongue and the teeth.

Oral insertion: Direct transoral insertion is rarely used. The tongue being one of the strongest muscles of the body pushes the bronchoscope as attempt to enter the larynx through the mouth is made. In a sedated patient the assistant can hold the tip of the tongue and pull it outwards to one side. The gag reflex is very difficult to suppress, and the oral route is much less comfortable for most patients. The angle of the larynx is more difficult than a nasal approach. A bite block should be used whenever oral route is used, because a bite on the bronchoscope can easily damage it.

The bronchoscope should be held straight without any curve (Fig. 6.3). Maintain a route along the midline to identify landmarks such as the uvula, the back of the tongue and the epiglottis. Avoid contact with the mucosa and the glottic apparatus as far as possible to minimize gagging and deglutition reflexes so that the anatomy and function of the vocal cords and surrounding areas can be examined properly.

Insertion through endotracheal tube: In patients with a preexisting endotracheal tube (already intubated), this route is used if the tube is big enough. The 3.5 mm bronchoscope can be passed through a 4.5 mm (I.D.) endotracheal tube with relative ease, but the patient will not be able to ventilate around the tube. A 5.5 mm or larger tube results in relatively little impediment to ventilation. Ultrathin instruments may be passed through smaller endotracheal tubes (3.0 mm or 3.5 mm tubes with 2.8 mm scopes and 2.5 mm tubes with 2.2 mm scopes). When using this approach make sure that the patient has a bite block between the teeth.

Insertion through tracheostomy tube: In patients with a tracheostomy tube, the bronchoscope may be inserted through the tube, through the stoma (after removing the tube), or through the larynx or behind and alongside the tracheal tube. As the circumstances warrant or allow. In some patients this may require temporary placement of a smaller tracheostomy or a 2.5 mm endotracheal tube through the stoma.

Insertion via Laryngeal mask airway(LMA): LMA is deployed when control of the airway, under general anesthesia, is needed, but endotracheal intubation is not required for passage of the bronchoscope. The size of LMA is chosen to accommodate a FFB appropriate for the child's or infant's airway.Even small size LMA will allow passage of a 3.5 mm bronchoscope (Fig. 12.21).

The procedure provides an optimal setting with maximal patient comfort.

Beyond the nasopharynx: As soon as the tip of the bronchoscope has passed the soft palate, the larynx should become visible. In many children there is significant amount of lymphoid tissue in the high posterior nasopharynx, and the passage beyond the choanus occasionally has to be made essentially blindly. The bronchoscope should be kept away from the posterior pharyngeal wall, and passed along the

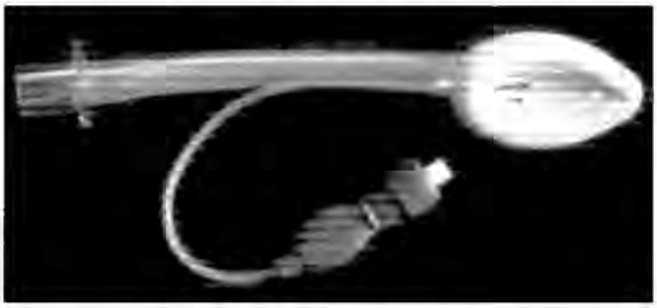


Fig. 12.21: Laryngeal mask airway

soft palate. After gaining some experience, it comes quite naturally. More lymphoid tissue may be seen at the base of the tongue, which often pushes the epiglottis posteriorly, hiding the rest of the larynx. It is better to spray the larynx with a bit more of local anesthetic when one first visualizes to prevent gagging and coughing. It requires several minutes after application of topical anesthesia (lignocaine) before the larynx becomes completely anesthetized, the delay is essential to ensure adequate anesthesia.

It is often possible to complete an adequate examination of the larynx and subglottic space without having to enter the trachea. However, unless there is a very good reason not to enter the trachea it is recommended that a complete examination of the upper and lower airways should be done. Repositioning the patient's head (flexing or extending the neck) may help to get a better angle of view. Because of the angles involved and flexible nature of the bronchoscope, you will occasionally not be able to obtain a satisfactory view of the immediate subglottic space, especially the posterior commisure. In such cases rigid laryngoscope may be needed.

When the larynx is adequately anesthetized, you are ready to pass through the glottis. Position the tip of the scope in the midline, just above the anterior commisure, flex the tip of the scope to reach this point. Then as the patient breathes in, decisively pass the instrument through the glottis, moving the tip posteriorly as you do so. The bronchoscope should be passed at least 2 cm into the trachea on the first passage. This is to avoid having the patient cough and hit the cords or other laryngeal structures on the tip of the bronchoscope. The subglottic space can be examined in a leisurely way on the way out, if necessary.

Once the bronchoscope is in the trachea. It may be necessary to spray a bit more topical anesthesia on the upper tracheal mucosa or the larynx, if the patient coughs violently or retches when you enter the trachea, it indicates requirement for more local anesthesia. Immediately instill approximately 1ml of solution through the bronchoscope and then withdraw the tip of the scope to above the larynx. Wait a few minutes before trying again. Remember, total dose of lignocaine used should not exceed 5-8 mg/kg(1% solution carries 10 mg/ml)

Examination of the Lower Airways

The first priority on entering the lower airway is t assess the patient's status. Quickly check the nee for additional local anesthetic, asses if the ventilatio and oxygenation is adequate. Note the dynamics o the trachea with respiration and the shape of th trachea. Are the cartilages normally shaped and an evidence of external compression, if present note it location and whether it is pulsatile. Advance th bronchoscope through the trachea to the carina avoid the wall of the trachea. Assess the state of th mucosa. Is it inflamed, edematous, or excoriated Excessive secretions should be suctioned if there i a suction channel. While suctioning always keep i mind the patient's comfort. Do not suction for prolonged period (suctioning too long can deflat the lungs). Sometimes thick tenacious secretions hav to be suctioned vigorously.

As you advance the scope along the airways, kee the tip centered in the airway, unless you hav specific need to view an area of the wall in detail As long as you keep in view of the airway ahea centered in the eyepiece, the bronchoscope wil follow easily without scraping the walls. This wil not only be more efficient, it will also reduce th possible friction and irritation of the mucosa an the probability of cough. The lower airways may b very sensitive and require additional amounts o topical anesthetic, but usually this is not required Patients with mucosal inflammation are more likel to need additional anesthetic.

The sequence of examination of the airways i entirely elective, but in general it is wise to examin the more normal areas first. Make a systemati examination of all the lobes and segments durin each examination unless there is a compelling reaso not to do so. Depending on the size of the patien and which instrument is used, it may or may not b possible to visualize each segment. Visualization i more likely in larger patients. The following guide lines should be followed while using the 3.5 m bronchoscope: - In infants less then 1 kg, it is usuall possible to visualize each of the lobar orifices, but i is difficult and unwise to go further into mainste bronchi. This is usually enough, however, to rul out major anatomic anomalies and to remove larg central mucus plugs. Infants between 1 and 2.5 k are somewhat variable, but usually it is possible t see at least the basilar segments clearly. Patients larger than about 2.5 kg usually are easily examined to a segmental level in the lower lobes, the middle lobe and the lingula, but the apical segment of the right upper lobe and superior segments of the left upper lobe may be difficult to visualize. Children larger than 6-8 kg should present little difficulty in visualizing the segmental airways of virtually all lobes, even without entering.

In patients of all ages the upper lobes are the most difficult to examine because of the extreme angulation required. Be aware that when the tip of the scope is maximally flexed, it may necessary to gently withdraw the bronchoscope in order to advance the tip towards its goal.

When using the 3.5 mm bronchoscope in children, it is quite easy to apply sufficient torque so that the tip may be directed anywhere. In larger patients, when the insertion cord is nearly completely inserted into the airway, or with larger bronchoscopes, it may be convenient to step to one side or the other of the patient's head in order to direct the scope into the opposite mainstem bronchus. After a certain level of experience and developing some skill most bronchospists are able to complete a thorough examination of all the lobes and segments in 30 seconds or less after crossing the glottis. Do not attempt to rush yourself during every procedure, but you should be able to perform a complete examination in a patient who cannot ventilate with the scope in the trachea. With prior oxygenation, virtually any patient can be apneic for 30 seconds.

Post Bronchoscopy Care of the Patient

Immediately upon completion of the procedure, assess the physiological status of the patient: respiratory rate, ventilation, heart rate, state of conscious, etc. Patient should be kept in a recovery room, the patient can be instructed that he may swallow and cough normally, even though he may feel he cannot, because of the local anesthesia. The patient should not be allowed food or drink until the effects of the topical anesthetic has completely disappeared, usually means 30 minutes after the procedure. Initially allow clear fluids and if they are able to accept it without vomiting they should be allowed normal diet.

Respiratory distress due to stridor or bronchospasm should be appropriately treated with oxygen nebulization and intravenous steroids as necessary

Patients who have been sedated should be observed until they are awake enough to at leas recognize their parents and swallow water withou difficulty. Appropriate monitoring procedures should be continued, depending on the age of the patient and the nature and depth of sedation, the nature of the underlying medical/surgical problem and the nature of the procedure. If a trans bronchia biopsy has been performed, for example a chest X ray should be ordered. Following diagnostic or therapeutic bronchopumonary lavage, some patients develop a transient fever. This usually is of little consequence and is self limiting. If a patient has had an uncomplicated procedure and has been only lightly sedated, he may be discharged shortly after the procedure.

Technical Problems During Bronchoscopy

Difficult Nasal Passage: Before insertion of the bronchoscope suction the nostril and posterior pharynx. If problem is encountered in entering a nostril the other nostril should be used. The nostri should be thoroughly aspirated of secretions and a topical vasoconstrictor may be used. Generally the middle meatus between the middle and lower turbinates is the path of least resistance. Looking into the patient's neck you should be able to see the light from tip of the bronchoscope. You should be able to see the light shining through the palate or the anterior part of the neck. The bronchoscope should be passed parallel to the floor of the nose and not directed towards the glabella. If the ligh from the tip can be seen near the glabella, it is likely that the instrument is directed in the wrong direction. If you feel you have inserted enough bu are unable to see the light withdraw the scope and look around if necessary withdraw the scope completely and make certain the lens is no obstructed with thick mucus. You meet a resistance in most patients. How much pressure to be exerted comers with experience. If you are able to see the passage ahead of the scope but are having problem getting the scope into pass a tight spot—wiggle and rotate the tip as you push ahead. Try an alternate passage i.e., the inferior meatus instead of the middle. If insertion is still difficult than use the other nostril.

Pharyngeal hypotonia: It is usually possible to approach the larynx directly, but sometimes the epiglottis is floppy and blocks the view. Two approaches are then possible: either pass down the posterior wall in the midline until past the epiglottis (take care not to disappear into the esophagus), or pass laterally alongside the epiglottis (take care not to get lost in the pyriform sinus) and then turn medially. It may also be helpful to change the angle of the patient's head and neck(more flexion or extension). The floor of the pyriform sinus is usually a different color from the surrounding tissue; it is white, and often has a prominent microvascular pattern, so it is easily recognized.

If the patient has been sedated deeply, relaxation of the pharyngeal musculature may make the larynx very difficult to find. This is true in-patients breathing through a tracheostomy tube (and some patients with endotracheal tube). Patients in whom it is difficult to see the laryngeal structures include those with large lymphoid tissues, neurological deficit, hypopharyngeal hypotonia and those with tracheostomy. Stimulating the patient will often increase the muscle tone and make the laryngeal structures more easily visible. In a patient with a tracheostomy, simply obstructing the tube for a few breaths will result in a marked increase in inspiratory effort and usually the glottis will then become visible. Alternately an oxygen line may be attached to the suction channel of the bronchoscope and oxygen insufflated at 1-3 L/min to distend the pharynx. While using the ultrathin bronchoscope, a suction catheter can be inserted through the opposite nostril and oxygen passed through the catheter to achieve the same result.

Difficult Laryngeal Passage

When a flexible bronchoscope is passed transnasally one must flex the tip anteriorly to approach the glottis. As the bronchoscope is advanced towards the glottis, the angulation of the tip must be constantly changed to keep the airway ahead centered in the view. Failure to retroflex the tip as the glottis is entered is a common cause of problems with the laryngeal passage. The most common problem, however is that the patient moves or closes the glottis whenever the bronchoscope comes near. This is usually due to either inadequate sedation or inadequate topical anesthesia and can be easily remedied.

Obstruction of Airway: In almost all children larger than 3.5 kg the 3.5mm bronchoscope will not obstruct the glottis sufficiently to produce respiratory distress. However, one must be adequately prepared for such a situation and always be alert to such a possibility. It is necessary to be certain that the patient is ventilating well before leaving the bronchoscope in the airway for any length of time.

Thick and Excessive Secretions: The suction channel of the 3.5 mm pediatric flexible bronchoscope is only 1.2 mm in diameter and thick secretions may be difficult to be suctioned. Instillation of a small volume of saline solution may loosen the secretions and facilitate their removal. Thick tenacious, at times rubbery mucus plugs may be removed by placing the tip of the bronchoscope into the mucus plug and applying the suction continuously, while withdrawing the bronchoscope slowly. This usually removes the mucus plug along with the bronchoscope. The occasional patient with very copious secretions might have to be given glycopyrrolate. A suction catheter can be placed through the other nostril and apply intermittent suction to the posterior pharynx. Glycopyrrolate is not effective for copious secretions from the trachea and the bronchi, this has to be suctioned. Remember to use the greatest available negative pressure on the suction tube as the suction channel is usually long and narrow. Suctioning should be brief so as not to deflate the patient's lungs. As long as it is clear that there is mucus occluding the lens and the tip is not against the mucosa, in which case you will see a red color it is appropriate to suction continuously. Judicious lavage with small volumes(3-5 ml) of sterile saline may be helpful.

Nasotracheal Intubation: Nasotracheal intubation over the flexible bronchoscope has found favour for difficult situations specially in neonates. The endotracheal tube (ET tube) is either advanced past the nares into the hypopharynx or placed all the way up on the hub of the flexible bronchoscope. The bronchoscope is then passed through the vocal cords to the midtrachea. With the carina visualised the ET tube is advanced down over the bronchoscope. Utilizing it as a guidewire, into the trachea. In an experienced hand it can be completed in 20-30 seconds. A common pitfall in this technique is to pass the endotracheal tube into the posterior nasopharynx prior to the passage of the bronchoscope into the ET tube. This severely restricts the mobility of the tip of the bronchoscope and ability to identify the laryngeal structures. Instead the ET tube should be placed over the bronchoscope and positioned as far proximally on the insertion cord of the instrument as possible. The tip of the bronchoscope should first be passed into the carina and then the Et tube passed through the nostril and glottis into the trachea. Unless the carina is kept in view during the entire procedure, the tip of the bronchoscope may inadvertently slip into the esophagus as the ET tube is positioned. The 3.5 mm flexible bronchoscope should be used with tubes ranging from 4.5 to 6 mm in diameter, the 4.9mm flexible bronchoscope(standard adult size with tubes of larger than 6mm and the Ultrathin flexible bronchoscope for tubes smaller than 4.0 mm.

Technical problems of the Bronchoscope: Clouding of the lens with mucus or blood: if lens is not cleared by a simple suctioning, inject 2-3 cc of sterile saline through the suction channel and suction. If this is not successful, try wiping the tip of the scope on the carina. As a last resort the bronchoscope may have to be removed the lens cleaned and reinserted.

Neonatal Flexible Bronchoscopy

With the availability of neonatal bronchoscopes with an outer diameter as little as 2.2 mm, smallest of neonates can undergo flexible bronchoscopy. There is considerable interest in direct visual assessment of the neonatal airway. Most of the indications are directed towards diagnosis and assessment of the airways and of severity of the abnormalities. The newer flexible bronchoscopes have an improved suction channel and more therapeutic maneuvers may be possible including aspiration of mucous plugs, instillation of drugs and satisfactory BAL. In a study by De Blic for 201 bronchoscopies in infants, the most common indications were persistent atelectasis, unexplained episodes of cyanosis, unexplained respiratory distress, stridor. The remainder were for acute atelectasis, assessment of lung malformations and repeat bronchoscopies for reassessment of the airways. In their study of 79 infants with ches radiograph abnormalities only 15 (19%) had norma findings with 22 (28%) having either tracheal or bronchial stenosis, 7 (9%) had granuloma, 10 (13% had vascular compression, the remainder had tracheo or bronchomalacia, hypersecretion and in one case an unsuspected foreign body.

Flexible bronchoscopy in neonates have a vita role in the evaluation of abnormalities of the upper airway including subglottic stenosis which compromise the respiratory status of the child in such a way that extubation from mechanical ventilation is difficult. The technique of blind insertion of a catheter remains the method of choice for obtaining lung secretions for microbiology, as it is simple to perform and minimizes the compromise to the infant.

Attention is paid to sedation and analgesia and comfort of the neonate. Inspection of the lower airway should always be performed after loca anesthesia of the larynx and sedation or genera anesthesia of the neonate. Local anesthetic such as 2% lidocaine should be used for spraying the voca cords. The infant must be monitored closely for any deterioration. Heart rate, oxygen saturation, blood pressure and temperature must be monitored constantly.

The bronchoscope can be inserted per nasally through a laryngeal mask or through the tracheostomy port. Risks of complications are significantly increased in severely ill infant requiring mechanical ventilation for respiratory failure. These babies are especially prone to hypothermia and therefore a warm environment and attention to the infant's temperature is essential. In ventilated infants, analgesia should be adequate. Benzodiazepine such as midazolam is usually used for sedation.

The airway of the sick preterm infant is readily compromized with the introduction of an instrument that almost completely blocks the endotracheal tube Video recording of the procedure is therefore necessary. The bronchoscope can be inserted and withdrawn within 10–45 seconds as tolerated by the infant and the video recording can be reviewed more closely for an accurate assessment of the findings Close inspection of the subglottic space is essential as this is often difficult to assess given the wide angle of a flexible bronchoscope.

After the procedure the infant requires close monitoring. Apneas, hypoxia and bradycardia are common and thus need to be sought and treated

For mechanically ventilated infants, blood gases are essential and the ventilatory parameters altered accordingly. Since any pre-existing laryngeal edema may be exacerbated by the procedure, the infant may require treatment with a short course of corticosteroid. Several special procedures can be performed even in small preterm infants through the working channel of the flexible bronchoscope. Interventional bronchoscopy however, is better performed using rigid bronchoscopes. Bronchoalveolar lavage although rarely done can be an important modality in neonates.

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CHAPTER

Pediatric Thoracoscopy

Sankaran Krishnan

In recent years, major technical advances have led to a profusion of minimally invasive surgical techniques, involving almost every organ system. This chapter summarizes the state-of-the-art in pediatric thoracoscopy and outlines the relative advantages and limitations of current techniques. Somewhat surprisingly, in some cases, thoracoscopic techniques can achieve therapeutic or diagnostic goals beyond the range of more conventional surgical approaches.

Thoracoscopy has been part of thoracic surgery for nearly a century. This technique allows the surgeon to operate in the thoracic cavity using a fiberoptic endoscope inserted through a small incision. Video-assisted thoracoscopic surgery (VATS) projects the endoscopic image onto television screens, allowing the entire operating team to view the procedure. With the recent explosion of interest in minimally invasive techniques, the role of thoracoscopy has expanded to include a wide range of procedures. Operations that previously required a large, painful thoracotomy incision can now be performed through small thoracoscopy ports. Hospital stays can often be shortened from weeks to days. Until recently, technological limitations put this technique out of reach of pediatric surgeons. Now, advances in miniaturization of instruments and improved optics allow pediatric surgeons to undertake a variety of procedures with this new diagnostic and therapeutic approach.[1-3]

HISTORY

The first recorded thoracoscopic procedure was performed in 1910 by a Swedish physician, Hans Christian Jacobaeus, who inserted a rigid cystoscope into the pleural cavity to lyse adhesions in a patient due to tuberculosis.[4,5] Thoracoscopy was subsequently used extensively for this indication during the first part of the twentieth century. Development of thoracoscopy as a diagnostic or therapeutic method stopped after the 1930s with development of effective antituberculous drugs. Advances in anesthesia and surgery permitted safe thoracotomy for resection, resulting in decreased interest in thoracoscopy. Although a few surgeons continued to use minimally invasive techniques for pleurodesis and diagnostic pleural biopsy, this approach was largely abandoned until recently when advances in instrumentation once again made it an attractive option.[6-8]

A number of recent developments have brought minimally invasive thoracic surgery to the forefront. The development of fiberoptic technology, an increasing variety of specialized instruments, improved anesthetic techniques including one-lung ventilation and improved video-assisted operative techniques have allowed surgeons to approach many clinical problems by thoracoscopy. Miniaturization of instruments, magnification, and improved optics have made it possible to apply these techniques to children. Thoracoscopy offers a number of advantages compared to open thoracotomy. Avoiding a large thoracotomy incision significantly reduces postoperative pain and disability. The incidence of wound complications is extremely low. Patients recover quickly and return to normal activities quickly, thus reducing hospital stay and health care costs. Finally, the small-port site incisions of thoracoscopy are cosmetically significant as compared to a large thoracotomy scar.

Pediatric thoracoscopy was not fully described until the 1970s. Prototype miniature instruments were introduced by Storz in 1969 and later used for pediatric laparoscopy by Gans and colleagues. The first report of pediatric thoracoscopy was by Klimkovich and colleagues in 1971.[8] In 1976, Rodgers and Talbert studied nine patients from 17 months to 16 years of age who underwent thoracoscopic biopsy of pulmonary parenchymal or mediastinal lesions. This series reported 100 percent diagnostic accuracy with no significant complications. Since that time, surgeons have expanded the use of thoracoscopic diagnosis and treatment to a wide range of pediatric thoracic diseases.

INDICATIONS FOR PEDIATRIC THORACOSCOPY

Biopsy or resection of mediastinal masses:

- Lymphoma
- Chronic inflammation or infection of mediastinal lymph nodes
- Bronchogenic cysts
- Thymoma

Biopsy of undiagnosed pulmonary infiltrates, lung masses, or pleural lesions:

- Infection
- Malignancy
- Metastases

Drainage and/or Decortication of Empyema

- Diagnostic and therapeutic treatment of pleural effusion:
  - Infection
  - Chylothorax
  - Malignancy
- Treatment of pneumothorax:
  - Resection of blebs
  - Pleurodesis
- Resection of congenital pulmonary and bronchogenic cysts
- Ligation of patent ductus arteriosus
- Esophageal procedures:
  - Esophagomyotomy
  - Resection of esophageal duplication
- Creation of pericardial window for pericardial effusion

Anesthesia[9,10]

Anesthetic technique is based on the anticipated procedure as well as age and size of the child. Although some short procedures in adolescents can be accomplished using regional anesthesia (multiple rib intercostal block or thoracic epidural), the vast majority of operations require general anesthesia. One-lung ventilation is almost always necessary, since complete collapse of the ipsilateral lung is needed for visualizing the lung and mediastinum and for maneuvering instruments.[10] For most patients one-lung ventilation can be accomplished using a standard double-lumen endotracheal tube. Neonates require selective main-stem bronchial intubation.[9] Spontaneous breathing and standard bilateral pulmonary ventilation with additional intercostal nerve blocks to facilitate light anesthesia can be used to avoid one-lung ventilation. All patients should undergo continuous electrocardiographic and oxygen saturation monitoring, along with intermittent blood pressure and temperature measurements. Invasive monitoring may be needed in select cases.

Procedure[11-13]

The standard thoracoscopic procedure involves initial placement of openings or "ports" for the telescope/camera and instruments. The exact location of port sites depends on the size of the patient. A small skin incision is made and the subcutaneous tissues are dissected bluntly until the pleural space is entered. A short cylindrical trocar port is then inserted for passage of the thoracoscope. The trocar is usually placed in the sixth intercostal space, with antero-posterior orientation determined by the site of the lesion (Fig. 13.1).

When the intrapleural space equilibrates with the atmospheric pressure, it creates a pneumothorax. Maintenance of adequate pneumothorax is crucial for visualization. Low pressure (4 mm Hg) carbon dioxide insufflation into the chest may sometimes be necessary to facilitate lung collapse, if one-lung ventilation or the standard technique is inadequate. The camera telescope is first inserted, the region of pathology visualized, and the remaining trocars can then be placed under direct vision.

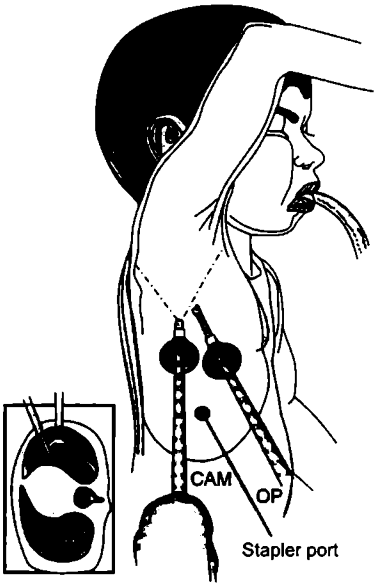


Fig. 13.1: Placement of port sites for camera and instruments for pulmonary biopsy. CAM, telescope camera port; OP, operative port

Pediatric thoracoscopy requires a wider variety of instruments than adult thoracoscopy. Most surgeons recommend three different-sized trocar diameters to accommodate differences in intercostal space size. A 0-degree telescope of appropriate diameter allows a direct end-on view and a 30-degree lens provides an angled view that allows the surgeon adequate vision. Most instruments (scissors, curved dissector, cautery, retractor, and atraumatic lung clamp) fit through the 3.75- or 5-mm ports. Some instruments, like the clip applier or stapler, however, require larger ports. Because of these limitations, procedures requiring these instruments (wedge biopsy or bullae resection, for example) can only be performed in children weighing more than 10 kgs.

Preoperative imaging with chest radiographs, transthoracic ultrasound imaging, computed tomography scanning, or magnetic resonance imaging is especially important in the pediatric patient. Adequate imaging allows for careful preoperative planning of positioning and trocar placement, depending on the lesion and the patient's size.

A three-person operating team is essential: Surgeon, first assistant, and nurse. A second assistant to move and focus the telescope camera is helpful. The surgeon stands on the side opposite the known pathology; the first assistant stands directly across the table. Television monitors should ideally be placed on both sides of the patient so that the surgeons and scrub nurse have an unobstructed view of the thoracoscopic image. At the end of the procedure, trocars are removed under direct thoracoscopic vision to ensure adequate hemostasis; a chest tube can be inserted through one of the sites if necessary. A pleural catheter is occasionally placed through the posterior cannula site for postoperative analgesia. The small chest wall port sites are closed in layers.

Complications[2,13,14]

Serious complications have been fairly infrequent in thoracoscopy. There are limited reports of complications in the pediatric population. Recently Rodgers reviewed a total of 173 pediatric cases in whom thoracoscopy was performed.[2,13] Overall mortality was 3 percent (6 patients) and complication rate was 9 percent (16 patients). Five of the six deaths occurred in patients undergoing thoracoscopic biopsy for diffuse interstitial lung disease. All these children had severe respiratory failure, and only one death in this group was related to the procedure itself. Complications included five pneumothoraces and four episodes of bleeding, none of which required reoperation.

There are no reports of infection, cardiac arrhythmias, air embolism, tension pneumothorax, or injury to intraabdominal organs with trocar placement in children.[2,13]

Contraindications to Thoracoscopy[2,13,15-17]

- Extensive pleural adhesions
- Extensive inflammatory process
- Previous pleurodesis
- Unresectable lesion
- Coagulation defect
- Inability to tolerate one-lung ventilation
  - Severe chronic obstructive pulmonary disease (COPD)
  - Dependence on mechanical ventilation with high peak pulmonary pressures
  - Absence of contralateral lung
  - Absence of contralateral pulmonary artery

- Hemodynamic instability
  - Hypovolemic shock
  - Cardiogenic shock
  - Inability to tolerate hypoxemia
- Conversion to open thoracotomy:[15]
  - Need for further resection
  - Pleural adhesions
  - Inability to find lesion
  - Lesion centrally located
  - Lesion too large for resection by thoracoscopy
  - Inability to obtain one-lung ventilation
  - Repair of perioperative injuries to thoracic structures
    - Electrothermal damage to major vessels
    - Inadvertent pericardial penetration
  - Lost needle, Excessive bleeding.

Thoracoscopy for Mediastinal Masses[18-20]

Diagnosis and treatment of mediastinal masses is one of the most common indications for thoracoscopy in both adults and children. Thoracoscopy is an excellent technique for biopsy and/or excision of these masses and allows the surgeon to visualize the entire hemithorax (unlike a limited open procedure). Thoracoscopy has been successful in diagnosing lymphoma, chronic inflammation, and infection in anterior hilar and superior mediastinal lymph nodes. Hilar, paratracheal, and subcarinal bronchogenic cysts can be dissected and excised. Management of posterior mediastinal masses with thoracoscopy remains controversial. Most larger masses in this population are neurogenic tumors and a more complete resection by open thoracotomy is often needed. Overall, thoracoscopy offers 85 to 100 percent diagnostic accuracy for mediastinal pathology in children.

A significant advantage of thoracoscopic biopsy is the shortened postbiopsy hospital stay, pain management and overall morbidity. In addition to the advantage of surveying the entire hemithorax, thoracoscopic biopsy of mediastinal masses offers significant improvement in post-operative morbidity. Most patients have minimal pain and are ready for discharge within 24 hours of the procedure. The major disadvantage of thoracoscopy is a limited ability to biopsy or resect deep seated masses.

Thoracoscopy for Pulmonary Infiltrates

Thoracoscopy is often used to biopsy nonresponding pulmonary infiltrates. It may especially be useful in immunocompromised patients as well as those who have failed treatment with broadspectrum antibiotics or have failed diagnosis with bronchoalveolar lavage. Thoracoscopic lung biopsy is generally rapid and may be performed under regional anesthesia in some cases.The EndoGIA stapler and EndoLoop (US Surgical, Norwalk, CT) are key to successful thoracoscopic lung biopsy. The stapler divides the lung tissue, securely closes the pulmonary defect, and provides hemostasis in one step. In smaller patients, this device is difficult to use, and the EndoLoop serves the same purpose. This instrument allows the surgeon to pass a loop of suture through a port to ligate the lung edge being sampled. As with mediastinal masses, thoracoscopic biopsy allows a complete survey of the hemithorax and access to all pulmonary lobes for identification and biopsy of abnormal areas that were undetected by preoperative imaging studies.

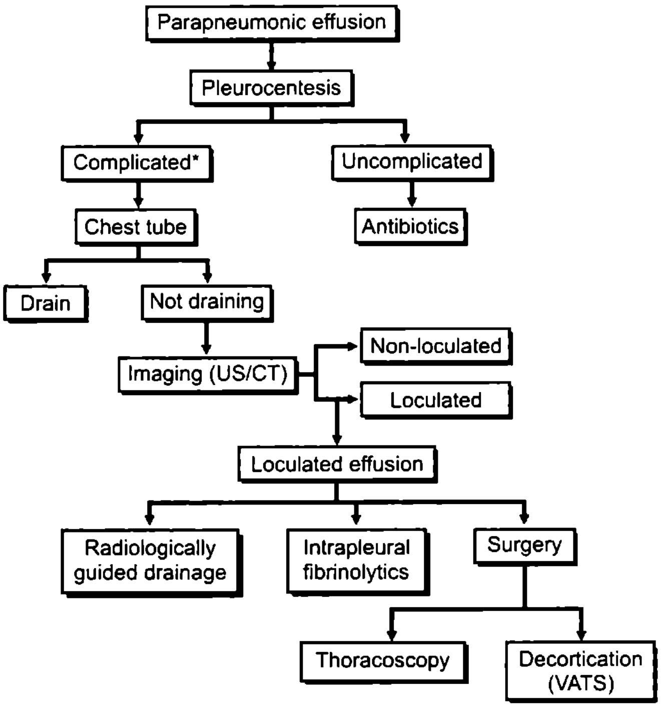
Thoracoscopy for Empyemas[21-24]

Thoracoscopy has been useful for treating children with early loculated empyema. In fact, where facility is available, it may be the procedure of choice. The treatment of childhood empyema has evolved over the years. This technique allows debridement and disruption of loculations under direct vision, providing complete drainage that is often impossible with simple tube thoracostomy. The procedure needs general anesthesia because of the discomfort associated with the debridement. Transthoracic ultrasound is used to locate the largest fluid collection preoperatively. Results suggest that early use of thoracoscopy to drain empyema may decrease the need for open thoracotomy and decortication in patients who fail standard chest tube drainage.

This is a summary of current strategy in complicated parapneumonic effusions/empyema in children.

Patent Ductus Arteriosus[25-27]

Thoracoscopy has recently been employed for ligation of patent ductus arteriosus (PDA). Laborde



*Complicated parapneumonic effusion: pH < 7.2, LDH > 500, glucose < 50.

and colleagues described a series of 38 patients, ages 1.5 months to 7.5 years, who underwent video-assisted PDA ligation. Two of these children required reoperation for incomplete closure. One child had recurrent laryngeal nerve injury, which subsequently resolved. Others have described this procedure in premature and young infants with a fairly high success rate. Despite the theoretical risk of uncontrolled hemorrhage during thoracoscopic dissection or ligation of the ductus, there are no reported episodes of bleeding in these patients. There are no deaths or significant complications in any series. Patients experienced minimal postoperative pain and most are discharged 24 to 72 hours after the procedure (excluding the premature infants). These preliminary studies suggest that this minimally invasive technique offers an effective alternative to open thoracotomy for children requiring PDA ligation. This approach however, remains controversial. Traditional thoracotomy for PDA ligation is a highly successful, well-tested procedure with minimal morbidity and mortality.

OTHER USES[28-33]

Pleural Effusion

The use of thoracoscopy for the evaluation and treatment of pleural effusion is used less commonly in children than in adults. It is sometimes used to evaluate effusions related to malignancy, pneumonitis and chylothorax. As with previous indications, thoracoscopy offers the advantage of a complete view of the entire hemithorax with minimal morbidity. Although the incidence of idiopathic pleural effusion is much lower in the pediatric population than in the adult, this technique may have a role in evaluating effusions that escape diagnosis by more conventional methods.

Pneumothorax

Thoracoscopy is currently used with much success in the treatment of recurrent spontaneous pneumothorax in otherwise healthy patients (or initial pneumothorax in patients with cystic fibrosis). After a preceding CT to evaluate presence of blebs and other pathology, the procedure is used to determine need for bleb ligation. Pulmonary blebs can be resected with the EndoGIA stapler or ligated with an EndoLoop ligature. Thoracoscopy is also an excellent option for all methods of pleurodesis: Talc insufflation, chemical pleurodesis, or mechanical abrasion. Talc insufflation is generally well tolerated with regional anesthesia and creates a dense pleural symphysis. Mechanical abrasion is the treatment of choice for cystic fibrosis patients, since it does not obviate lung transplantation at a later date.

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CHAPTER 14

Radiology for the Pediatric Intensivist

Praveen Khilnani, Michael Hartenberg

The beginning of medical imaging in the pediatric intensive care unit (PICU) dates back to the use of a portable roentgenographic unit at the bedside. It was used to obtain a chest roentgenogram, an abdominal roentgenogram, a skull roentgenogram, or an extremity film in a patient who was acutely or desperately ill and in no condition to be moved to the radiology department. Although obtaining a portable radiograph of the chest or abdomen is still the most common examination, technical improvements have been made, that have resulted in better images from much better machines. The new portable units are smaller, more compact, more powerful, more easily moved, and unfortunately much more expensive.

Other imaging modalities in addition to the basic radiograph have resulted from the recent rapid growth in electronics and the development of computer technology. NOT only many new means of diagnosis are available, but several are portable and can be performed at the bedside. These newer imaging techniques include real-time and Doppler ultrasonography, the use of radionuclides, single photon emission tomograph (SPET), positron emission tomography (PET), computerized tomography (CT), and magnetic resonance imaging (MRI).

We will concentrate on three commonly used imaging techniques for pediatric patients; Ultrasonography, Computerized Tomography, and Magnetic Resonance Imaging. Issues of transport to the radiology department will be discussed and finally radiological investigations of common conditions seen in critically ill children will be discussed. Echocardiography is discussed in a separate chapter.

Ultrasonography (USG)

One of the biggest and most significant developments has been the evolution and improvement of the real-time ultrasound machine. Ultrasonography is well established as the primary imaging modality in the evaluation of the infant brain for evidence of structural defects or the presence of abnormal defects such as hemorrhage or for determination of the status of the ventricular system, as long as the anterior fontannel is open. Ultrasonography is not good for evaluation of extra axial bleeding. The use of ultrasonography in the abdomen as an affordable screening procedure requiring no radiation and providing cross sectional images is well known and accepted. In the small infant the status of the kidneys can be readily determined, and an obstructive process, such as marked hydronephrosis secondary to ureter-pelvic junction obstruction or posterior urethral valves can be easily diagnosed. In addition ultrasound guided renal biopsy can be performed. Adrenal hemorrhage, abdominal tumors, such as neuroblastoma or Wilms' pyloric stenoisis, duodenal atresia, or even intussusception, are all conditions that can be diagnosed by ultrasonograpy. Ultrasonography of the chest can be particularly useful for the evaluation of opaque hemothorax and pleural effusion. Pleural or pericardial aspiration may be assisted by ultrasonography or echocardiography.

Although patency of the aorta and inferior venacava can be determined by real-time ultrasound, Doppler ultrasound is emerging as the non-invasive diagnostic procedure of choice in the evaluation of circulatory abnormalities. It has been extended *in utero* to evaluation of the fetus and the umbical vessels and postnatally to the major abdominal vessels, especially the portal and renal vessels in conjunction with the inferior vena cava and the aorta. This non-invasive procedure may prove to be the examination of choice when questions are raised about the patency of the flow pattern in any major vessel, particularly when angiography may be technically difficult or the status of the patient may be precarious and a contraindication to transport from the PICU to a remote angiography suite.

It is of critical importance to realize that both real-time and Doppler ultrasound are highly operator dependent. An ultrasound machine can be compared to a violin because both require a highly trained, talented specialist to produce diagnostic images or beautiful music, respectively, whereas in untrained or poorly skilled hands the same equipment may produce inadequate nondiagnostic images or only noise.

The most frequently requested ultrasound studies in pediatrics are to determine the status of neonatal heads, particularly after traumatic deliveries or seizure-type activity to ascertain the presence of intracranial hemorrhage or some focal abnormality. Next in frequency are abdominal studies carried out to evaluate the liver, spleen, adrenal glands, pancreas, or kidneys or the status of the major vessels for a variety of clinical situation ranging from trauma to major organs to evolution of a possible mass. Acutely ill, particularly those on ventilators, may be difficult to transport, so, often the ultrasound studies are performed at the bedside using more sophisticated and compact, equipment which has benefitted greatly from recent advances in both electronics and computer technology. Esophageal doppler echocardiography has been used to assess cardiac output in critically ill patients.

Small portable ultrasound (GE, sonosite) machines are available to help pediatric intensivist with non invasive detection of atelectasis, pneumothorax, pericardial as pleural effusion, poor cardiac contractility and locating femoral or subclavian vein during central line placement.

Computerized Tomography (CT) (Fig. 14.1)

Main indications for CT scan in a pediatric intensive care situation include:

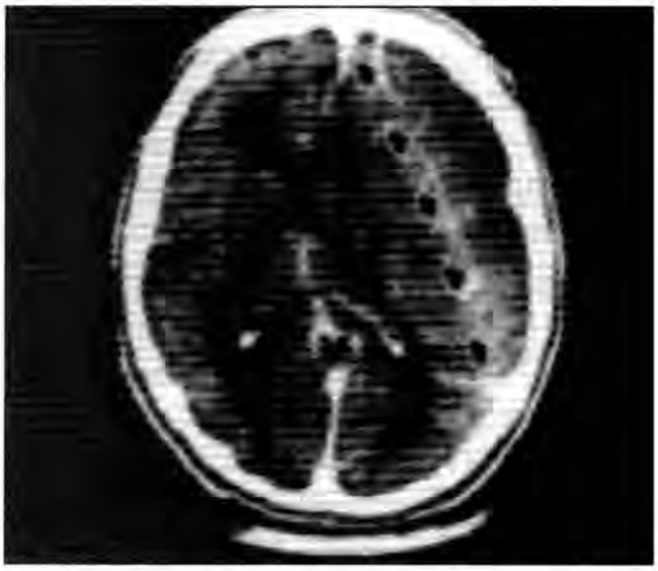

Fig. 14.1: Subacute subdural hematoma: CT scan of brain demonstrating large isodense mass over left cerebral convexity compressed cerebral cortex shows enhanced density delineating inner border of subacute subdural hematoma Normal structures are shifted across midline

1. Evaluation of trauma
2. Evaluation of bleeding
3. Evaluation of tumor
4. Evaluation of abscess.

Head chest and abdominal CT scans are frequently done for the above indications. Transport of the patient to Radiology Department is required. Intravenous sedation may also be required. The resolution of CT is inferior to MRI, however CT can be used as a good initial test on an emergency basis. If a detailed examination is required, MRI can be done when the patient is clinically more stable. Helical (spiral) CT is fast and gets done in few minutes. Bone windows can be used to obtain clear picture of skull fractures, specially depressed skull fractures. High resolution CT (HRCT) is helpful for chest and abdomen, specially for lung lesions. Nature of tissue, such as blood, fluid, fat, calcium, bone, can be easily delineated. Recently CT scan of the chest has been done in patients with acute respiratory distress syndrome to see the extent of posterior/basilar consolidation not evident on routine radiographs. In addition color subtraction CT images can be used to assesss airway compression due to masses or vascular rings. In empyema and pneumatoceles, exact location of consolidation, pus, pleural thickening can be appreciated.

Magnetic Resonance Imaging (MRI)

Currently MRI of the head is used most frequently in pediatrics followed by MRI of the spine, chest, abdomen and extremities. Primary indications for MRI of the head in pediatric intensive care include evaluation of seizures, meningoencephalitis, tumor, intracranial hemorrhage, cerebral ischemia and abscess particularly in areas of posterior fossa and brain stem. MR angiogram (MRA) can be peformed to evaluate cerebrovascular abnormalities. Contrast enhancement of basilar meningeal inflammation (exudates) is helpful in diagnosis of tubercular meningitis or meningoencephalitis. Cysticircus lesions can be clearly seen. The patient has to be transported to Radiology, the examination is relatively long and requires sedation or even anesthesia. Any patient movement during MRI examination distorts the images, therefore, a still patient is required. While the resolution of images is excellent the main limitation of MRI is technical. Since the MRI room has a strong magnetic field, ferromagnetic metals (watch, ring, stethoscope, mechanical ventilators circuit valves) are not allowed in the room therefore, special compatible anesthesia machines and pulse oximeters are necessary. In pediatric patients safety during sedation for MRI is a major issue and endotracheal intubation and resuscitation equipment must accompany the patient. Ketamine, midazolam and propofol are useful agents for sedating a child for MRI.

Patient Transport

The problem of transporting PICU patients raises several critical care questions and relates directly to the several more complicated imaging modalities for which bringing the equipment to the child is not an option. This problem applies specifically to CT, MRI and angiography. Who accompanies the patient from the PICU to one of these remote destinations is usually determined by the severity of the child's illness and need for ventilatory support. PICU nurse and the physician trained in pediatric resuscitation and sedation is needed to accompany a particularly ill or unstable patient. Each case must be considered on an individual basis and special scheduling must be arranged with the imaging facility to provide prompt and efficient handling of such critical patients.

Problems are unique to the specific imaging modality, as exemplified by MRI for which transfer to a special nonmagnetic cradle is necessary and metal equipment cannot be taken into the room containing the scanner without disastrous consequences for the magnet. Ventilatory support and close observation within the magnet are difficult and the required scanning times are much longer than those necessary for CT studies.

Since CT can be performed more easily and quickly, is relatively less expensive, and is usually more readily available as an emergency procedure, it is done more frequently than MRI, even though CT requires ionizing radiation and MRI does not. Ninety percent of emergency CT scans are of the head and frequently involve PICU patients either on the way to or from the emergency room, PICU and/or the operating room.

In the following section, radiological investigation for various conditions commonly encountered by the pediatric intensivist will now be discussed.

Head Trauma

Routine skull radiography following minor head trauma is to be discouraged. The examination of choice to exclude significant intracranial abnormality is computed tomography (CT).

Plain-film skull examination would seem to have several advantages over the CT scan.

a. Less ionizing radiation.
b. Less expensive.
c. Easier to perform in younger patients
d. More readily available.

It also has one major disadvantage—the information they provide is rarely of clinical significance.

The presence of a nondepressed linear skull fracture does not indicate the need for medical intervention. The absence of a nondepressed linear skull fracture does not preclude the presence of significant intracranial abnormality. In serious head trauma, plain-film examinations may be more useful but still have a somewhat limited role relative to CT.

Skull films (frontal and lateral) may be helpful in localizing a radiopaque foreign body when a penetrating-type injury is suspected.

If the physical examination is usually compromised by soft tissue swelling, skull films (frontal, lateral, and appropriate tangential views) may help characterize the extent of a depressed skull fracture more fully.

A horizontal beam, lateral skull radiograph may be useful when looking for the presence of an air-fluid level in the sphenoid sinus. This may be an evidence of a basal/skull fracture.

Neither routine skull radiography at the time of injury nor CT will accurately predict which patients are likely to develop a leptomeningeal cyst (growing fracture) following skull fracture.

Reliance on skull radiography will be misleading, in those patients who experience significant intracranial injury, in the absence of a skull fracture.

Croup and Epiglottitis

In patients with typical croup or with typical epiglottitis, radiographic examination has a relatively insignificant role. Direct visualization of the supraglottic structures is discouraged in those patients with an uncertain diagnosis and the lateral neck radiograph may prove diagnostic. Patients with epiglottitis are at risk of complete airway obstruction at any moment. One should not delay management of patients with strong clinical suspicion of epiglotitis. *Establishment of a suitable airway is far more important than the acquisition of a confirmatory lateral neck radiograph.*

The filming sequence is as follows:

A single portable lateral neck radiograph should be obtained in as much upright position as is tolerated by the patient. Excessive cervical extension is to be discouraged, as this may precipitate further airway compromise. If the epiglottitis is shown to be normal, additional views may then be obtained. If the lateral neck is not diagnostic of croup, frontal films should also be obtained, looking for symmetric compromise of the subglottic airway.

Chest (Fig. 14.2)

The standard radiographic examination of the chest include both frontal and lateral views. Depending on the age of the patient and the degree of cooperation, examination can be either upright or supine. Oblique views can be obtained for further delineation of the retrocardiac or perihilar regions. They can also be helpful when distinguishing thymu from a suspected upper lobe pneumonia.

The decubitus chest radiograph can be used to evaluate pleural fluid collections:

- If there is unilateral diaphragmatic elevation, the ipsilateral decubitus view can evaluate for a hidden subpulmonic effusion. Bilateral decubitus views can help detect the presence of small pleural fluid collections. Ipsilateral decubitus views can help distinguish a loculated pleural process from a mobile pleural fluid collection.
- If the entire hemithorax is opaque, a decubitus view will rarely help distinguish pleural disease from parenchymal disease. Chest sonography should be considered in this clinical situation. The decubitus view can better define questionable parenchymal densities seen on films with suboptimal inspiratory efforts. It can also be used to evaluate the question of focal air trapping as might be seen with an aspirated nonopaque foreign body. To obtain a decubitus chest radiograph, the patient is placed side down against a firm, flat surface. The radiographic beam is then projected parallel to the floor. The "down" lung is compressed by the weight of the thorax and tends to be radiographed as might be expected with exhalation. The "up" lung tends to be radiographed during inspiration. The typical aspirated foreign body does not cause blockage to air entry and therefore does not typically cause an airless pulmonary segment (atelectasis). It more typically impedes air movement during

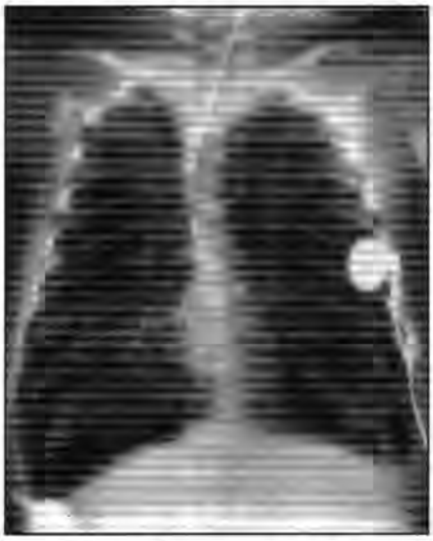

Fig. 14.2: Chest X-ray: Bronchopulmonary dysplasia (BPD

exhalation, at which time the airways are less fully distended. This causes one pulmonary region to remain inflated as the others deflate during exhalation. This leads to unilateral air trapping, if a main stem bronchus is involved, or localized air trapping, if the foreign body has been aspirated into a more peripheral bronchus. Both decubitus views should be obtained when searching for evidence of an aspirated foreign body. This enables the radiologist to compare lung regions for their compressability. A false-positive examination can be obtained in the asthmatic patient with asymmetric air trapping due to nonuniform mucous plug distribution.

A false-negative examination can be seen in some patients with nonopaque foreign body aspiration. In the child with a strong clinical history of foreign body aspiration, a normal radiographic examination should not deter direct bronchosopic examination.

Abdomen (Fig. 14.3)

Abdominal radiography is difficult to outline because of the enormous range of diagnostic consideration. Vomiting, diarrhea, constipation, and gastrointestinal (GI) bleeding can all be caused by a wide variety of disorders, most of which do not lead to specific plain-film abnormalities.

The filming sequence is as follows Radiographs of the supine abdomen (KUB) are obtained. When the supine radiograph shows multiple dilated loops of bowel, it can be difficult to distinguish distal mechanical obstruction from generalized ileus. A prone abdominal radiograph or a prone cross-table view of the pelvis should then be obtained. If gas can be demonstrated through to the rectum, a significant mechanical obstruction is unlikely. The gasless abdomen is a nonspecific radiographic finding that can be a manifestation of intestinal obstruction. A significant obstruction in the upper GI tract will prevent entry of swallowed air, causing a relatively gasless abdomen. If the obstructed loops of bowel are fluid filled rather than air filled, the abdomen will also be relatively gasless.

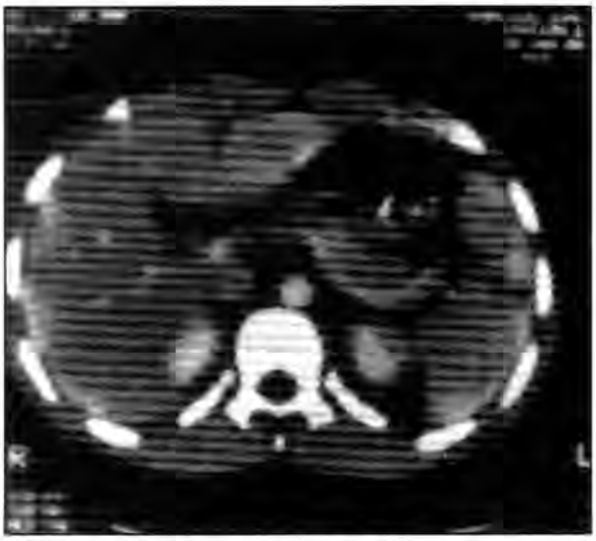

Fig. 14.3: Abdominal CT: Splenic tear

Upright abdominal radiographs infrequently add information regarding pneumoperitoneum and intestinal obstruction. If the supine abdominal film is not diagnostic of pneumoperitoneum, an upright chest radiograph is much more likely to confirm pneumoperitoneum than a lateral view.

Intestinal air-fluid levels are not diagnostic of bowel obstruction.

An air-fluid level merely indicates the presence of air and fluid in the same loop of bowel at the same time. They can also be seen in patients with gastroenteritis or with adynamic ileus. If obstruction is suspected clinicallly but the plain-films are nonspecific, contrast examination of the bowel may prove necessary. The type of examination will depend on the clinical situation.

Hypertrophic Pyloric Stenosis

The child who presents with projectile nonbilious vomiting during the first months of life is suspected of having hypertrophic pyloric stenosis.

If physical examination identifies the hypertrophied muscle as a small palpable tumor in the upper abdomen, no radiographic examination is necessary. If the clinical presentation is atypical or if the physical examination is equivocal, radiologic examination should be undertaken.

The filming sequence is as follows:

- *Abdominal sonography (ultrasound):* Criteria have been established for the sonographic diagnosis of hypertrophic pyloric stenosis. Sonography does not require the use of ionizing radiation and can be performed portably if necessary. If sonography is not available or if the pyloric measurements are not considered diagnostic, an upper gastrointestinal (UGI) series should be obtained.

UGI series and a preliminary abdominal film should be obtained to evaluate the intestinal gas pattern before contrast is introduced. A nasogastric tube should be used to ensure safe control of the quantity of contrast introduced. Barium sulfate suspensions is generally an acceptable contrast agent. Water soluble (Gastrograffin) contrast is given if patient has severe reflux or chances of aspiration.

Intussusception

The classic triad of cramping abdominal pain, palpable mass, and bloody *"currant-jelly" stool*, is only seen in a relatively small number of patients with intussusception. In those patients with a less typical presentation, a high index of suspicion is often necessary to make the diagnosis. In the "usual" age group (6 months to 2 years), the intussusception is usually ileocolic, with a variable length of ileum invaginating into a variable length of colon. Lead points are infrequently found in the "usual" age group and may be very difficult to identify during the initial radiographic evaluation. Patients outside the "usual" age group have higher incidence of lead points.

Follow-up examinations may be necessary in these children to exclude an underlying bowel abnormality. Although some intussusceptions may reduce spontaneously, those that are not reduced will lead to vascular compromise and eventually bowel infarction. The filming sequence is as follows:

Supine and prone abdominal radiographs are obtained. If there is a clinical suspicion of perforation, a supine horizontal beam film should also be obtained to exclude pneumoperitoneum. (In the older child, an upright frontal chest film will serve the same purpose.) Although the plain-film examination may suggest the presence of an intussusception by defining a paucity of ascending colon gas and/or the presence of an unusual intraluminal defect, the plain-film examination rarely excludes the presence of intussusception. A normal abdominal radiograph does not exclude the presence of intussusception. Enema examination is generally encouraged. Some institutions encourage surgical reduction of all intussusceptions.

Enema examination serves the purpose of diagnosis and no attempt is made at hydrostatic reduction. Barium sulfate suspension is generally an acceptable contrast agent. If bowel integrity has been questioned, a water soluble contrast agent would be preferred.

Other institutions encourage the radiologist to attempt hydrostatic reduction of the intussusception. To facilitate the enema examination, sedation of the patient is helpful. Gentle but constant pressure is kept on the contrast column in an attempt to untelescope the intussuscepted bowel. Barium sulfate suspension is usually an acceptable contrast agent, but water-soluble contrast agents may be used at the discretion of the radiologist if there is concern for bowel perforation. The only absolute contraindication to enema examination is the presence of peritonitis. The presence of a small bowel obstruction pattern on plain-film examination suggests the presence of a long-standing intussusception. Although chronicity implies a lesser success rate with hydrostatic reduction, this is only a relative contraindication. If there is clinical suspicion that the intussusception is long-standing, a water-soluble contrast agent would be preferred. Reported success rates for hydrostatic reduction vary widely, depending on the length of the symptomatic period, the presence or absence of a lead point, and the age of the patient.

Computed Tomography and Blunt Abdominal Trauma

The advent of the CT scan and the emphasis on conservative management for solid organ injury has changed the radiographic approach to a child with blunt abdominal trauma. Traditional examination may have included the following tests:

- Plain-films of the abdomen,
- Radionuclide imaging of the liver and spleen,
- Intravenous urography,
- Limited UGI with water-soluble contrast agent.

Blunt abdominal trauma can cause multiple organ injuries, even though they are not all clinically apparent at the time of trauma. It is increasingly apparent that solid organ injuries may be amenable to conservative management with watchful waiting and non-invasive radiographic studies replacing surgical intervention in some cases.

Computed tomography has proved a good screening test for the integrity of solid organs. Both

CT and real-time sonography can be used for subsequent imaging of lesions not thought to require surgical managements at the time of injury.

It is difficult to establish definite criteria for those patients who will benefit from body CT and those patients who will not benefit from body CT in the emergency department setting. Each child's trauma is a nonreproducible event, making controlled experimental studies very difficult to perform. It is obviously not appropriate to subject all pediatric patients to extensive tomography following blunt abdominal trauma. Patients with abdominal trauma and significant associated, head trauma may be evaluated as follows:

- Physical examination of the abdomen is typically quite difficult in these children; radiographic assistance in their evaluation may be very helpful in the acute situation. It may be advantageous to perform both the body tomography and the CT scan of the head at the same time.
- Computed tomography and intravenous urography are useful tools in the Emergency Department setting, intravenous urography can quickly identify the presence of two functioning kidneys. If only a single kidney is identified, a significant contralateral renal pedicle injury is suspected, and further evaluation is immediately required. Detection of renal contusion or incomplete renal laceration will be limited in some emergency department settings, if plain-film tomography is not available. Computed tomography has the advantage of screening the other upper abdominal viscera and peritoneal space simultaneously. Nonpedicle injuries may be easier to characterize with cross-sectional imaging. As conservative management of nonpedicle injuries becomes more popular, however, this "advantage" may prove relatively insignificant for ultimate patient management.
- Except for the logistics of patient transportation, there are no major disadvantages to performing CT relative to intravenous urography.

Child Abuse

- A normal skeletal survey does not exclude child abuse.
- An abnormal skeletal survey does not "prove" child abuse.

Even with the above caveat, a skeletal survey can provide clinical and legal information regarding previous episodes of skeletal injury and should be performed with liberal indications. Our survey consists of frontal and lateral views of the skull, the spine, and the chest, single frontal views of the pelvis and the extremities. These views should be supplemented by full radiographic examinations of any specific bone or joint of clinical or radiologic concern. Radionuclide bone imaging will add to the overall detection of bone lesions in certain children, particularly those with nondisplaced rib fractures.

The physes are normally sites of "increased" tracer concentration in the child with unfused epiphyses. Unless meticulous attention is directed to these regions, metaphyseal corner fractures may go unnoticed on scinti graphic skeletal examination. Certain skeletal survey features suggest child abuse:

- Multiple fractures in different stages of healing,
- Fractures involving bones not typically broken in children or in a specific age group of children.,
- Fractures believed to have an unusual causal mechanism, such as spiral fractures or fractures involving the metaphyseal corners.
- Any fractures out of proportion to the clinical history.
- Metabolic bone disease that may be an indication of nutritional neglect.

There are also nonskeletal injuries that may be detected radiographically.

a. Pulmonary parenchymal abnormalities from blunt thoracic trauma.
b. Visceral and mesenteric damage from blunt abdominal trauma.

FURTHER READING

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Section Two

Respiratory System

CHAPTER

15

Respiratory Physiology

Praveen Khilnani

It is essential to understand basic respiratory physiology to understand and manage the disease process involving the lungs, upper or lower airways, alveoli or all of the above. In addition understanding of central regulation of respiration as well as neuromuscular factors affecting the respiratory mechanics is as important.

Basic Respiratory Physiology

The purpose of the lung is to exchange oxygen and carbon dioxide across the alveolar capillary membrane.

Growth of the distal airway lags behind that of the proximal airway during the first five years of life. The relatively narrow distal airway until age five years presumably accounts for the high peripheral airway resistance in this age group. The relative weakness of cartilaginous support in infants compared to adults may lead to dynamic compression of the trachea in situations associated with high expiratory flow rates and increased airway resistance such as bronchiolitis, asthma or even crying. After birth, there is a dramatic increase in the number of alveoli. At birth, 20 million; by age 8, 300 million. After age 8, it is not clear whether alveolar multiplication continues or it is just the alveolar enlargement. At birth, alveolar surface area is 2.8 square meters. By 8 years of age, the alveolar surface area has increased to 32 square meters. Adult alveolar surface area is 75 square meters. In infants, diffusing capacity is only 1/3 to 1/2 of that of adults even when normalized to body surface area.

Collateral ventilation in adults takes place by interalveolar pores of Kohn, bronchioalveolar channels which are Lambert's channels and interbronchiolar channels.

Collateral ventilation starts happening sometimes after the first year of life. Lambert's channels start appearing around six years of age. Interbronchiolar channels have been found in diseased lungs only.

Airway Resistance

In children, peripheral airway resistance is four times higher than that of adults or older children. In adults, the majority of airway resistance comes from upper airway, particularly the nose. This explains why lower airway obstructive disease is much more common in infants secondary to inflammation, which makes them symptomatic.

- Distribution of inspired gas.
- Dead space ventilation.

Dead space could be anatomical, physiological dead space or alveolar dead space.

Anatomical dead space cannot participate in gas exchange.

Physiologic dead space is equal to anatomic dead space plus the alveolar dead space.

Normal dead space to tidal volume ratio is 3 (VD/VT).

Physiological dead space can be calculated by:

$$PaCO_2 - PeCO_2 \times \frac{\text{Minute ventilation}}{PaCO_2}$$

(e = expired)
(a = arterial)

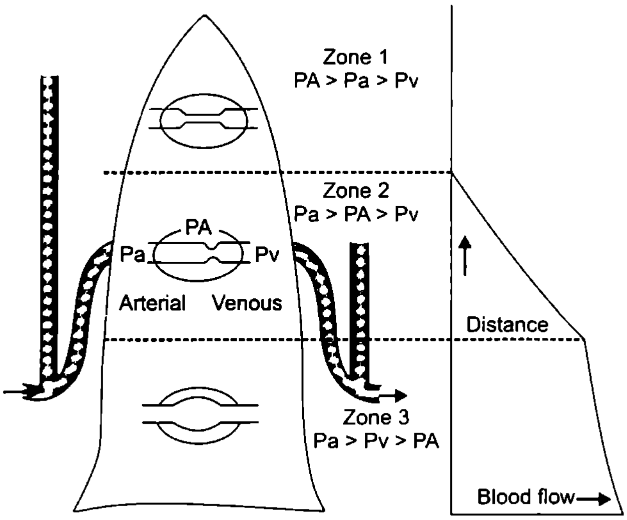

Fig. 15.1: Zone of perfusion in the lung

(Redrawn from West JB Dollery CT, Naimark A: J Appl Physio 1964;19:713)

Three zones in the lung that are physiologically different, have been defined by West (Fig. 15.1).

In West zone 1, the alveolar pressure is higher than the arterial pressure, is higher than venous pressure.

In West zone 2, the arterial pressure is higher than the alveolar pressure, is higher than the venous pressure.

In West zone 3, the arterial pressure is higher than the venous pressure, is higher than the alveolar pressure.

Dependent alveoli at the base of the lungs expand more for a given change in pressure. This is fortunate because the greater portion of pulmonary blood flow also goes to dependent lung regions.

However, if the alveoli in the dependent regions get too small, they could collapse. Closing capacity is defined as the sum of the closing volume, and the residual volume.

PEEP (positive end expiratory pressure) is designed to raise the FRC(functional residual capacity) above the closing capacity.

Children younger than six years of age have a closing capacity greater than FRC in supine position. This is due to reduced elastic recoil of the lungs.

Transpulmonary Pressure

During breathing, the transpulmonary pressure must be generated in order to overcome the opposing forces of the elastic recoil as well as the force due to frictional resistance to gas flow. The inertial force of respiratory system is negligible.

Compliance

Compliance is change in volume per unit change in pressure. Lung compliance depends on the elasticity of lung tissue and on initial lung volume before inflation. Stiff lung means low compliance, expansile lung means high compliance.

Greater pressure gradient must be generated in order inflate a lung from a very low lung volume.

Therefore, specific compliance is the lung compliance per unit FRC.

Specific compliance in newborn and adult is the same. Reciprocal of total compliance equals to the reciprocal of chest wall compliance plus the reciprocal of lung compliance.

- Elastance is reciprocal of compliance.
- Pressure is equal to flow times resistance.

In laminar flow, the resistance varies inversely with the 4th power of the radius. In turbulent flow, the resistance varies with the 5th power of the radius.

In turbulent flow, density of the gas is more important than the viscosity.

Helium/oxygen mixtures having very low density have been used in upper airway obstruction. Helium/oxygen mixture has a lower density than air oxygen.

Conductance is the Reciprocal of Resistance

In BPD (bronchopulmonary dysplasia) and Alfa 1 antitrypsin deficiency, because of poor cartilageous support, airway collapses when active expiration occurs.

Time constant (resistance x compliance) is the time needed for the lung unit to reach 63 percent of its final volume. Slow alveoli take longer to fill so they have a longer time constant. That could be due to either their resistance being too high or their compliance being high.

Given a particular time constant resistance would then be inversely proportional to the compliance.

Laplace equation is pressure equals two times the surface tension divided by the radius R. It predicts that small alveoli empties into larger ones resulting into the ultimate collapse of small alveoli, and over distention of larger alveoli.

Surfactant lines the walls of the alveoli and prevents collapse. Therefore, one needs smaller distending airway pressure to keep alveoli open.

Pulmonary blood flow is best at FRC (functional residual capacity), approximately at lung volume of 120 ml. (Fig. 15.2). At lower lung volume, the teethering action of the tortuous vessels causes vascular resistance to go up, and at higher volumes physical compression of the vasculature occurs, thereby increasing the vascular resistance.

At both, too low and too high volumes, the pulmonary blood flow is poor. Pulmonary blood volume is increased in the supine position. Average values of pulmonary artery pressure are 22/8 mm Hg with a mean of 15 mm Hg.

The difference between the pulmonary arterial pressure and the left atrial pressure is the driving pressure for the pulmonary blood in the vascular tree.

Ventilation (V) Perfusion (Q) Ratio

During positive pressure ventilation, the driving pressure is pulmonary arterial pressure minus the pulmonary alveolar pressure. Apical regions of the lung are underperfused, therefore VQ (ventilation is three times more than perfusion) ratio is about 3. Basal regions are somewhat underventilated, so VQ ratio is 0.6.

Shunt

Shunt refers to the venous blood that has traveled from right side of the circulation to the left side without ever coming in contact with the ventilated lung. Therefore, VQ ratio is 0.

Examples of shunt include: normal bronchial and thebesian circulations, or blood flow through the collapsed lung, and cyanotic congenial heart disease with blood flow from the right side of the heart to the left side. Figure 15.3 shows ISO shunt diagram. Increasing inspired oxygen concentration will usually compensate for small areas of shunting in the lung. Note if the shunt is 50 percent (say if one lung is collapsed, getting only perfused but not ventilated, and the other lung is normally ventilated and perfused, even 100 percent oxygen will not achieve > 80 mmHg arterial PaO_2.

Dead space: means there is ventilation, but no perfusion to that space. VQ ratio is equal to infinity.

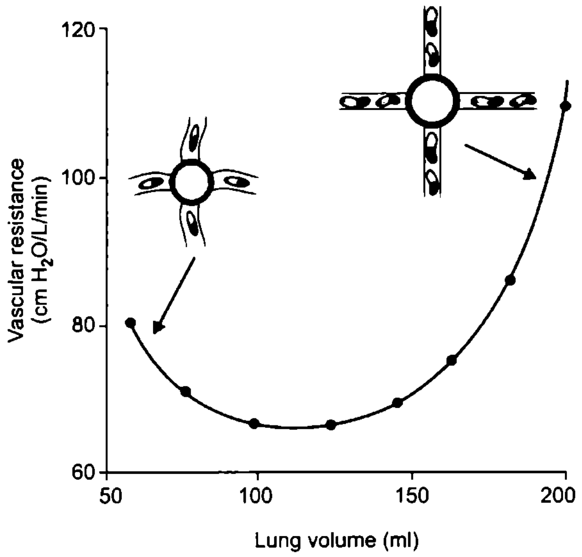

Fig. 15.2: Relationship between lung volume and vascular resistance

(Redrawn from West JB: Blood flow. In: Respiratory physiology—the essentials, Baltimore, 1979, Williams & Wilkins).

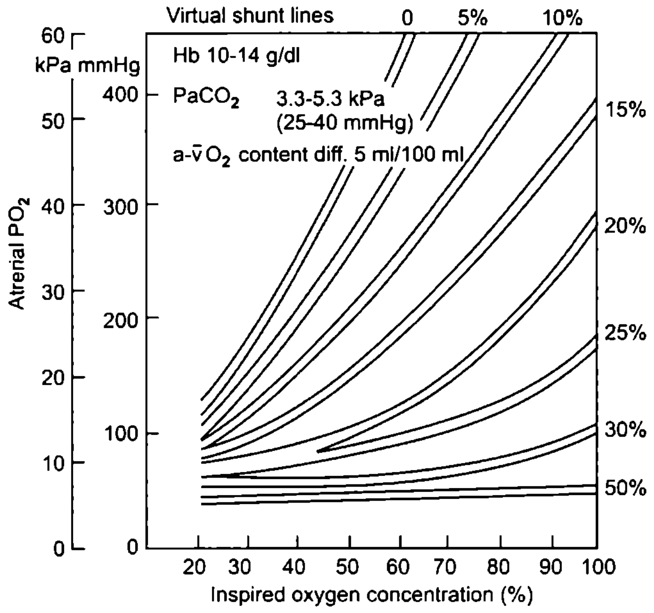

Fig. 15.3: ISO shunt diagram. The ISO shunt bands are widened to include the indicated range of $PaCO_2$ and hemoglobin (HB)

(From Benatar SR, Hewlett AM, Nunn JF: Br J Anaesth 1973; 45:711).

At 25 percent of shunt, 100 percent oxygen can get the PaO_2 as high as 150, but at 50 percent shunt, 100 percent oxygen will not raise the PaO_2 above 80-90.

Arterial pCO_2 equals alveolar ventilation divided by CO_2 production.

A large admixture of venous blood to the pulmonary capillary would produce only a small increase in the arterial pCO_2. Normal term newborn has a lower PO_2 than the adult. The reason for that is increased venous admixture which probably arises mainly from a combination of right to left shunting through persistent fetal vascular channels, and at atelectatic areas of the lungs.

Diffusing Capacity

It is equal to flow divided by the driving pressure. Diffusing capacity increases with age, height and body surface area reflecting the increase in diffusing capacity with increasing total surface area available for diffusion.

The rate of flow of fluid in the lungs is equal to the difference of capillary and interstitial hydrostatic pressure minus the difference in plasma and interstitial oncotic pressures. Hydrostatic pressure gradient drives fluid into the interstitium and oncotic pressure gradient tries to keep the fluid intravascular.

Hydrostatic pressure can be increased by increasing blood volume, increasing left atrial pressure, increasing pulmonary blood flow from a large left to right shunt. Pulmonary edema usually does not develop until the capillary hydrostatic pressure will go more than 25 mm of mercury beyond the normal oncotic pressure. Hydrostatic pressure in the interstitial space is believed to be somewhat negative under normal circumstances. Hypoproteinemia, even though it will reduce oncotic pressure, usually does not cause pulmonary edema as long as alveolar capillary membrane is intact.

Lymphatic channels in the interstitial space clear the excess interstitial fluid and protein. This is an important safety mechanism, when overwhelmed in congestive heart failure or with lymphatic obstruction due to injury to the lymphatic channels secondary to Fontan operation, it may result in pulmonary edema/effusion.

Oxygen Carriage

Hemoglobin is the main carrier (HbO_2 saturation) of O_2/1.34 ml/gm. PaO_2 is O_2 tension exerted by oxygen in physical solution in plasma (0.003 ml/mmHg paO_2), responsible for gradient for oxygen to bind with hemoglobin.

Term newborns have 70 percent hemoglobin F and 30 percent hemoglobin A. By the end of the first six months of life, hemoglobin A has replaced hemoglobin F and only trace levels of hemoglobin F are detectable. The P 50 for Hemoglobin F is 19 compared to P 50 of 27 (the PaO_2 level at which the hemoglobin is 50 percent saturated) for hemoglobin A. Acidosis, increased 2, 3 diphosphoglycerate (2, 3 DPG) (stored blood has depletion of 2, 3 DPG) shift the oxyhemoglobin dissociation curve to right, meaning easier dissociation of oxygen from hemoglobon (Fig. 15.4). Fetal hemoglobin binds tightly to oxygen (curve shifted to left). Hemoglobin S defers from hemoglobin A by the substitution of valine for glutamic acid at position six. Hemoglobin S has a lower P 50. Meth hemoglobin cannot bind oxygen.

If the percentage of meth hemoglobin is more than 30-40 percent, the patient becomes symptomatic. 1 mg/kg of 1 percent methylene blue can be given.

The affinity of CO to the hemoglobin molecule is 210 times greater than the affinity of oxygen for hemoglobin. In modern blood gas analyzer O_2 saturation is often claculated using a measured oxygen tension and assuming a normaly placed oxyhemoglobin-dissociation curve. If the curve is shifted to the right or left, the calculated value of saturation will be different than the true measured value. The major source of error is that blood gas

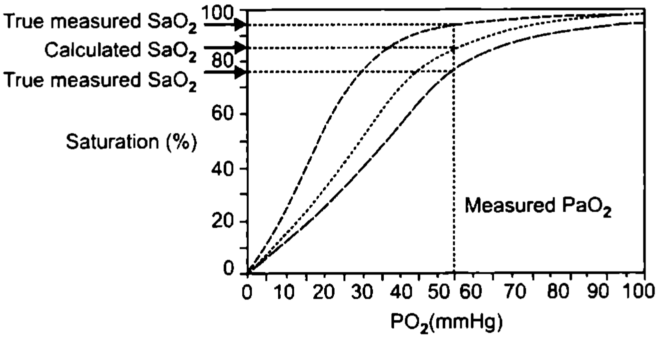

Fig. 15.4: Oxyhemoglobin-dissociation curves

analyzers assume a normal concentration of 2.3-DPG and thus a normally placed curve.

Carbon monoxide increases the binding of oxygen for hemoglobin and does shift the position of oxyhemoglobin dissociation curve to the left. It also decreases peripheral utilization of oxygen.

Critical tissue level of mitochondrial PO_2 is thought to be around 1 mm of mercury.

Critical jugular venous oxygen saturation is 24 percent, because less than 24 percent results in unconsciousness.

Oxygen extraction ratio is the ratio of oxygen consumption to oxygen delivery.

It can be calculated by arterial venous oxygen content difference divided by arterial oxygen content. Normal extraction ratio is 25.

Control of Respiration

Three respiratory control centers exist:

- Pneumotaxic center, Apneustic center and the Medullary center.
- Medullary center is located in the medulla and is most important for respiration.
- Pneumotaxic center fine tunes inspiration to expiration.
- Both Pneumotaxic and Apneustic centers which are located in the pons are not necessary for normal control of respirations.

Chest Mechanics

Diaphragmatic fatigue in premature infants may be explained because of longer contractions and longer relaxation time and less sarcoplasmic reticulum in the muscle fibers, and therefore, a need of more substrate for contraction and relaxation.

Chest wall in newborns is more compliant, therefore, gets sucked in with each inspiratory movement if there is respiratory distress, and therefore work of breathing is more.

Infants breathe more close to their closing capacity.

Hypoxia depresses CO_2 response in newborns. Hypoxia alone also depresses ventilation more so in premature neonates. Phrenic nerve paralysis causes more trouble in newborns compared to adults because the intercostal stabilizing mechanisms are not that good. Thus unilateral phrenic nerve paralysis in the infant develops into a massive flail ches because the paralyzed diaphragm and ribs are al sucked into the chest with active inspiration. C-spin injury at the level below C5 may result in respirator compromise because even though function of th diaphragm remains intact, paralysis of intercosta muscles causes severe chest wall retraction durin active inspiration. Respiratory muscles perfor approximately half their work on inspiration Respiratory muscles have to overcome tissue elasti resistance. The second major source of resistance i friction generated by the gas flowing through th airways. A combination of these two determine how much total work inspiratory muscles have t do. Hypoventilation leads to hypercarbia an hypoxia with hypoventilation PaO_2 falls first slowly and then rapidly as the alveolar ventilation falls Furthermore, with the raised inspired oxyge pressure or a lower oxygen consumption, eve greater degrees of hypoventilation would be neede to produce alveolar hypoxia.

APPLIED RESPIRATORY PHYSIOLOGY FOR MECHANICAL VENTILATION

Mechanical ventilation in children and neonates i different from adults.

While basic principles of Physics and gas flo apply to all age groups, anatomical and physiologica differences play a significant role in selecting th type of ventilator as well as the ventilatory mode and settings.

Upper airway in children is cephalad, funnel-shape with narrowest area being subglottic (at the level o cricoid ring), as compared to adults where the uppe airway is tubular with narrowest part at the voca cords.

Airway resistance increases inversely by 4th powe of radius, i.e. in an already small airway even on mm of edema or secretions will increase the airwa resistance and turbulent flow markedly necessitatin treatment of airway edema, suctioning of secretion measures to control secretions.

Low functional residual capacity (FRC :Volume o air in the lungs at end of expiration) reduces th oxygen reserve, reduces the time that apnea can b allowed in a child.

Respirations are shallow and rapid due to predominant diaphragmatic breathing and inadequate chest expansion due to inadequate costovertebral bucket handle movement in children. Therefore a child tends to get tachypneic rather than increasing the depth of respiration in response to hypoxemia.

Oxygen consumption/kg body weight is higher therefore tolerance to hypoxemia is lower.

Susceptibility to bradycardia in response to hypoxemia is also higher due to high vagal tone.

Pores of Kohn and channels of Lambert (brocho alveolar and interalveolar collaterals) are inadequately developed making regional atelectasis more frequent.

Closing volumes are lower and airway collapse due to inadequate strength of the cartilage in the airways is common making a child particularly susceptible to laryngomalacia, and tracheo-bronchomalacia as well as lower airways closure.

Therefore, children tend to require smaller tidal volumes, faster respiratory rates, adequate size uncuffed endotracheal tube, adequately suctioned clear airway for proper management of mechanical ventilation.

Gradient between mouth and pleural space is the driving pressure for the inspired gases and this gradient is needed to overcome resistance and to maintain alveolus open, by overcoming elastic recoil forces.

Therefore, a balance between elastic recoil of chest wall and the lung determines lung volume at any given time. Normal inspiration is actively initiated by negative intrathoracic pressure driving air into the lungs. Expiration is passive.

Ventilation

Ventilation washes out carbon dioxide from alveoli keeping arterial $PaCO_2$ between 35-45 mm of Hg. Increasing dead space increases the $PaCO_2$.

$$PaCO_2 = k \times \frac{\text{Metabolic production}}{\text{Alveolar minute ventilation}}$$

Alveolar MV = respiratory rate x effective tidal volume

Effective TV = TV – dead space

Dead space = Anatomic (nose, pharynx, trachea, bronchi) + Physiologic (alveoli that are ventilated but not perfused)

Adequate minute ventilation is essential to kee $PaCO_2$ within normal limits.

Oxygenation

Partial pressure of oxygen in alveolus (PAO_2) is th driving pressure for gas exchange across th alveolar-capillary barrier determining oxygenation

PAO_2 = ({Atmospheric pressure – water vapor} × FiO_2) – $PaCO_2$ / RQ

RQ= respiratory quotient

Adequate perfusion to alveoli that are well ventilated improves oxygenation.

Hemoglobin is fully-saturated 1/3 of the wa through the capillary.

Hypoxemia can occur due to:

a. Hypoventilation
b. V/Q mismatch(V – ventilation, Q – perfusion)
c. Shunt(perfusion of an unventilated alveolus, atelectasis, fluid in the alveous)
d. Diffusion impairments

Hypercarbia can occur due to:

a. Hypoventilation
b. V/Q mismatch
c. Dead space ventilation

Gas Exchange

Hypoventilation and V/Q mismatch are the most common causes of abnormal gas exchange in the PICU.

One can correct hypoventilation by increasing minute ventilation.

One can correct V/Q mismatch by increasing amount of lung that is ventilated or by improving perfusion to those areas that are ventilated.

Pulmonary capillary flow is best at the functional residual capacity(FRC).

Overdistension of alveoli causes compression of caillaries reducing the flow (Q is low, ventilation, V is high, so V/Q mismatch approaching dead space ventilation), and lower lung volume (below FRC) also cause kinking of capillaries reducing the capillary flow (Q is relatively low, with unventilated alveoli, blood is shunted).

So, depending on ventilatory pressures (or tidal volumes, PIP, PEEP) and lung perfusion (cardiac output, volume status, PEEP, etc.), these West zones (as discussed earlier) will change, especially during supine or prone positioning.

This leads to the understanding of oxygenation (depending on percentage of shunt) or ventilation (depending on the dead space) and the ventilation of perfused alveoli.

SUMMARY

As evident from above discussion, children are not miniature adults. A knowledge of the physiologic differences is important to properly understand the principles of mechanical ventilation in pediatric patients. Respiratory bronchioles, alveolar ducts and alveoli grow in number until 8 years of age, and continue to grow in size until adulthood. Pores of Kohn connecting alveoli are not developed until 1 year of age, and channels of Lambert which connect alveoli to larger airways do not develop until 5 years of age. This results in poor collateral gas circulation in the airways and alveoli. In children, the majority of airway resistance lies in lower airways as compared to adults where nasal passages alone may be responsible for 60 percent of total airway resistance. Furthermore, due to softer cartilage supporting the airway, collapse of the airway is more common with relatively smaller changes of airway pressure. Children have a relatively small functional residual capacity (volume of air in the lungs at the end of normal expiration), and a higher oxygen consumption compared to adults. Therefore, normal children tend to have relatively shallow breaths at a rate higher than adults. When a child is in respiratory distress, the respiratory rate increases ultimately progressing to slowing respirations, progressing to gasping followed by apnea or cardio respiratory arrest. It is therefore, extremely important to recognize tachypnea, agitation, nasal flaring, grunting, retractions as early signs of hypoxemia and respiratory failure. Cyanosis, lethargy and bradycardia are late signs dangerously close to cardiorespiratory arrest.This must and can be avoided by early recognition and appropriate intervention.

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CHAPTER

16

Oxygen Therapy in Pediatrics

Satish Deopujari, Suchitra Ranjit

Oxygen therapy is the most important aspect of supportive care in the management of a critically ill child. Knowledge of the physiology of oxygenation is a key to the proper oxygen therapy. High flow systems are more dependable devices for oxygenation and their use needs to be stressed.

Patients on oxygen need close monitoring. Ventilatory support and CPAP is mandatory in some patients in addition to oxygen therapy for the prevention and treatment of hypoxia.

Oxygen is one of the most essential elements in the body but surprisingly there are no stores of oxygen (there is no physiological explanation to this fact ......). One molecule of glucose yields 32 molecules of ATP in presence of oxygen but the same glucose yields only 2 molecules of ATP in its absence and in addition yields lactic acid.

Definition

Increasing the concentration of oxygen in the inspired air to correct or prevent hypoxia is oxygen therapy.[1]

Arterial oxygen tension (PaO_2) of less than 60 mmHg beyond the age of 28 days of life is defined as Hypoxemia. Hypoxemia in neonates is defined as PaO_2 of less than 50 mmHg.[2]

Physiology

Knowledge of physiology of oxygenation is important for proper oxygen therapy. The concept of partial pressure, saturation and content of oxygen is dealt with in the lines to come.

Partial Pressure of Oxygen

Atmospheric pressure at sea level is 760 mmHg. Oxygen constitutes 21 percent of air and thus the partial pressure of oxygen is around 160 mmHg at sea level (21% of 760 mmHg). Partial pressure of oxygen in the alveoli PAO_2 (note the capital A) is 110 mmHg. Oxygen is inhaled from the environment into the alveoli and from there to blood and tissues depending on its partial pressure.

For all the practical purposes partial pressure of oxygen in the alveoli can be calculated as.

$$PAO_2 = FiO_2\,(P_B - 47) - 1.2\,(PaCO_2)$$

PB = Barometric pressure, 47 = water vapor pressure

Partial pressure of oxygen is important for:

1. Driving oxygen from the environment to the mitochondria (Driving pressure)
2. The saturation of hemoglobin.

The partial pressure of oxygen in arterial blood (PaO_2, note the small a) is measured by a blood gas machine. Oxygen molecules dissolved in plasma (i.e. not bound to hemoglobin) are free to impinge on the measuring oxygen electrode. These free oxygen molecules are noted as the partial pressure of oxygen. PaO_2 is a function of the alveolar PO_2 and the alveolar-capillary interface. Arterial PaO_2 (small 'a') gives us valuable information about the status of gas exchange within the lungs, provided it is subtracted from the calculated alveolar PAO_2 (note the capital A).

Saturation of hemoglobin is measured by pulse oxymeter (SpO_2). An instrument known as co-oxymeter can directly measure the saturation of arterial hemoglobin, an *in vitro* measurement called as SaO_2. Saturation of hemoglobin depends on the partial pressure of oxygen. The relationship between the saturation and PaO_2 is not linear but S shaped and is known as the oxygen dissociation curve. The curve denotes that when the PaO_2 falls below 60 mmHg hemoglobin saturation rapidly declines and thus it is imperative to maintain saturation above 90 per cent (Fig. 16.1). The concept of saturation of hemoglobin and partial pressure can be compared to a transport bus. The seats in the bus are analogous to hemoglobin and the oxygen to passengers. If the bus has 12 (12 gm. Hb/100 ml of blood) seats and all seats are occupied the saturation is 100 per cent. With bus having only 7 seats and all seats are occupied the saturation is still 100 per cent but the number of passengers in this bus are less, a situation akin to anemia. In a patient with hemoglobin of 6 gm% and if all his hemoglobin is to carry oxygen the pulse oxymeter will show a saturation of 100% but the amount of oxygen per 100 ml of blood is obviously less. With a low PaO_2, hemoglobin carries less oxygen and the saturation is less, depending on the oxygen dissociation curve. Patients with polycythemia, the situation is like a bus with more number of seats say 18, even if 80% of these seats are occupied there will be enough oxygen in the blood. Remember the only person who will take the bus from one place to the other is the driver (The PaO_2). Please see Figure 16.1.

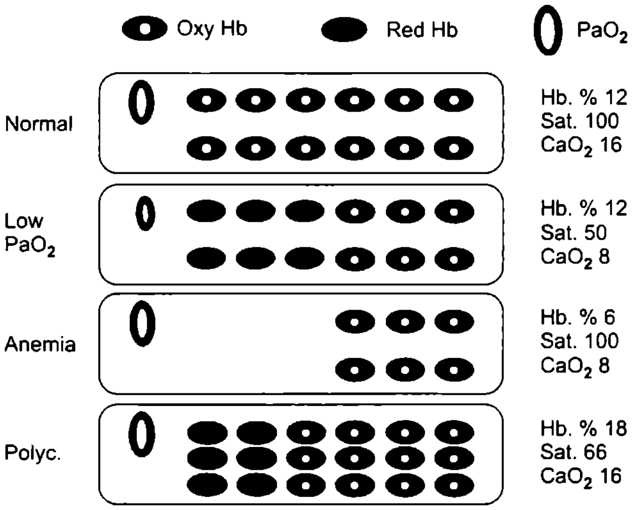

Fig. 16.1: Effect of PaO_2, Hb concentration, oxyhemoglobin saturation on oxygen content (CaO_2) in different conditions. Polyc. (Polycythemia)

CaO_2 = (Hb. × 1.34 × SaO_2) + (PaO_2 × .003 ml)

Content of Oxygen in the Blood

The amount of oxygen carried by the hemoglobir can be calculated or actually measured and is determined mainly by the saturation and the amoun of hemoglobin. Normally 100 ml of blood contair 16 to 20 ml of oxygen and is a prime indicator o hypoxemia. Content of oxygen (CaO_2) is calculatec by the following formula.

CaO_2 = (Hb. × 1.34 × SaO_2) + (PaO_2 × .003 ml)

(Hb. × 1.34 × SaO_2) = Oxygen bound to hemoglobin

(PaO_2 ×.003 ml) = Oxygen dissolved in plasma

As was mentioned earlier, patient with sever anemia will have less amount of oxygen for a giver amount of saturation. Content of oxygen for hemoglobin of 15 gm per cent and 10 gm per cent is showr in Figure 16.2. Oxygen transport to the tissues occur in two ways:- either dissolved in plasma (PaO_2) o bound to hemoglobin molecules (SaO_2). Th relationship between SaO_2 and PaO_2 is the oxyger dissociation curve.

Most of the oxygen is carried in the blood bounc to hemoglobin (98.5%). Once the hemoglobin is full saturated, increasing the PaO_2 will not significantl increase the content of oxygen in blood as it wil only increase the amount of dissolved oxygen.

Hypoxemia and Hypoxia

Reduced oxygen content of the blood is hypoxemia whereas impaired oxygen utilization by the tissue is hypoxia. It is possible to have hypoxia inspite o normal amount of oxygen in the blood and th reverse is also true.

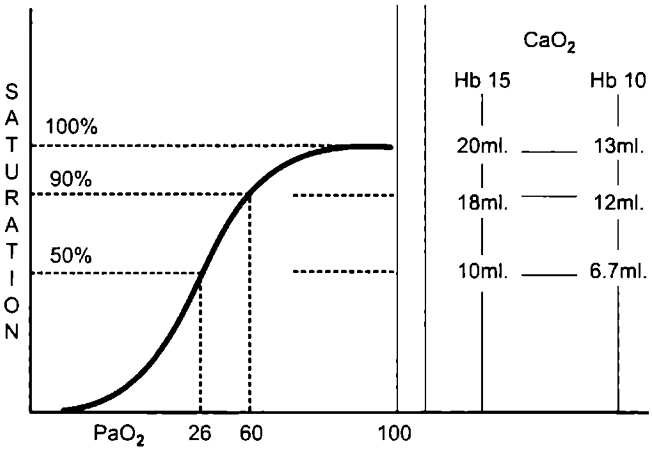

Fig. 16.2: Relationship of Hemoglobin, PaO_2, saturation and oxygen content (CaO_2)

The goal of proper oxygenation is the adequate supply of oxygen to the tissues. Supply of oxygen to the tissues is a combined function of the content of oxygen in blood and that of cardiac output. Patients with anemia carry less amount of oxygen in blood but are not always necessarily hypoxic because the delivery of oxygen to the tissues is achieved by increasing the cardiac output.

Recognition of Hypoxia

Oxygen delivery to tissues depends on the adequate ventilation, gas exchange, and circulation (Fig. 16.3). Tissue hypoxia occurs within 4 minutes of failure of any of these systems.

The successful treatment of tissue hypoxia requires early recognition. This is difficult since the clinical features are often nonspecific and include altered mental state, dyspnea, cyanosis, tachypnea, arrhythmias, and coma.

Central cyanosis is an unreliable indicator of tissue hypoxia (It is detectable when the concentration of reduced hemoglobin is about 1.5 gm/100 ml of blood rather than the widely quoted value of 5 gm/100 ml of blood).[3]

The causes of tissue hypoxia can be grouped into two broad categories:

1. Those causing arterial hypoxemia
2. Those causing failure of the oxygen-transport system without arterial hypoxemia.

Hemoglobin saturation as measured by pulse oxymeter (SpO_2) and PaO_2 (Measured by blood gas machine) are readily measured parameters and remain the principal indicators for initiating, monitoring, and adjusting oxygen therapy. However, PaO_2 and SpO_2 can be normal when tissue hypoxia is caused by the low output cardiac states, anemia, and failure of tissues to utilize oxygen.

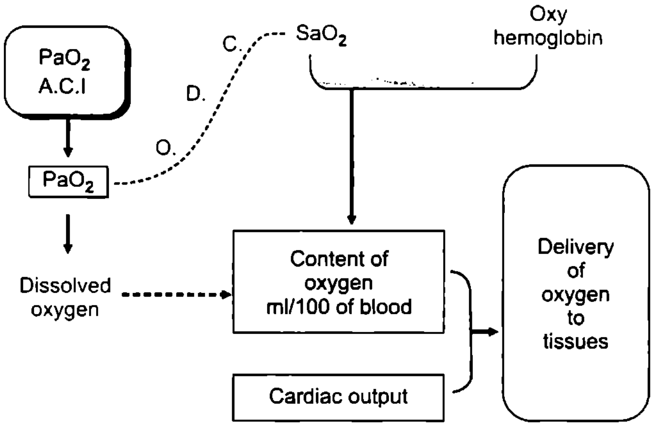

Fig. 16.3: Factors affecting oxygen delivery A.C.I. (Alveolar capillary interface), ODC (Oxygen dissociation curve)

Types of Hypoxemia

Type A is characterized by low oxygen tension in alveoli (PAO_2). A low PAO_2 can result from:

1. Low barometric pressure
2. Low fraction of inspired oxygen (FiO_2)
3. Hypercarbia—elevated partial pressure of carbon-dioxide in the arterial blood ($PaCO_2$).

Low barometric pressure occurs at high altitudes. Low FiO_2 is rarely a problem, since inspired air is nearly always composed of 21 per cent oxygen and 79 per cent nitrogen. Even at the top of the Mount Everest, FiO_2 is normal (21%), it is the barometric pressure that is low.

Type B is characterized by an elevated alveolar-arterial oxygen tension gradient (AaG). The AaG is the difference between the PAO_2, as computed from the alveolar gas equation, and the PaO_2, as obtained from the arterial blood gas analysis.

$$AaG = PAO_2 - PaO_2$$

AaG is a useful index of oxygen exchange in the lung. Normal individual breathing room air, AaG is 10 mmHg. AaG varies with FiO_2. Causes of elevated AaG are:

1. Ventilation/perfusion mismatch
2. Pulmonary or cardiac shunt
3. Decreased mixed venous oxygen saturation.

Oxygen Delivery Devices

Oxygen is a drug and should be prescribed in proper doses, with proper mode of delivery and needs to be monitored while being administered. The administration of oxygen to the patients require the selection of an oxygen delivery system that suits the patient's size, needs, and the therapeutic goals. Oxygen delivery systems are essentially categorized as either *low-flow or high-flow systems.*

1. *A low-flow system* provides an FiO_2 that varies with the patient's inspiratory flow.
2. *A high-flow system* provides a specific FiO_2 at flows that meet or exceed the patient's inspiratory flow requirement.

The patient's actual flow requirement depends on his minute ventilation and his I:E ratio.[2]

- Normal flow requirements are three to four times the minute ventilation.
- Minute Ventilation = Tidal Volume × Respiratory Rate
- Normal tidal volume is around 6 ml/kg.
- Thus, a 10 kg child breathing 60 times a minute with an assumed I:E ratio of 1:2 (his minute ventilation will be 3.6 l/min.) needs around 12 lit/min of oxygen or air-oxygen mixture.
- Some of the commonly used devices for oxygen delivery are discussed below.

Nasal cannula consists of two soft prongs that arise from the oxygen supply tubing. The prongs are inserted into the patient's nares, and the tubing is secured to the patient's face. Oxygen flows from the cannula into the patient's nasopharynx, which acts as an anatomical reservoir. The fractional concentration of inspired oxygen (FiO_2) varies with the patient's inspiratory flow. In a newborn baby, nasal cannula delivers 24 to 45 per cent FiO_2. Flowmeters capable of delivering 0.125 lit/min are effective in achieving a concentration of approximately 28 to 30 percent.[4-6]

Maximum flow accepted through a nasal cannula is 2 lit/min and the humidification of oxygen is not necessary for this flow.[5]

Improper size cannula can lead to nasal obstruction or irritation. Inadvertent CPAP may be administered depending upon the size of the nasal cannula and the rate of gas flow.

Nasopharyngeal catheters are soft tubes with several distal holes. The catheter should be inserted into the patient's nose to a depth, slightly above the uvula. Oxygen flows from the catheter into the patient's oropharynx, which acts as an anatomical reservoir. The FiO_2 varies with the patient's inspiratory flow.

Improper insertion can cause nasal or pharyngeal trauma. Excessive flow can produce pain in the frontal sinuses. Excessive secretions and/or mucosal inflammation can result in occlusion of distal openings.

Simple oxygen masks are plastic reservoirs designed to fit over the patient's nose and mouth and can be secured around the patient's head by an elastic strap. A reservoir effect is produced by the internal capacity of the mask. Holes on each side of the mask provide an egress for exhaled gases and serve as room-air entrainment ports. The FiO_2 varies with the patient's inspiratory flow.

Aspiration of vomitus may be more likely when a mask is in the place. Rebreathing may result in accumulation of CO_2 if O_2 flow is inadequate.

Partial-rebreathing masks are similar to simple oxygen masks but contain a reservoir at the base of the mask. The reservoir receives fresh gas plus exhaled gas approximately equal to the volume of the patient's anatomical dead space. The oxygen concentration of the exhaled gases combined with the supply of fresh oxygen, permits the use of flows lower than those necessary for other devices (e.g., non-rebreathing masks), and potentially conserves oxygen use.[5]

Non-rebreathing masks are similar to partial-rebreathing masks but they do not permit the mixing of exhaled gases with the fresh gas supply. A series of one-way valves placed at the reservoir opening and on the side ports ensures a fresh oxygen supply with minimal dilution from the entrainment of room air. This design provides a higher FiO_2 than the simple and partial-rebreathing masks. See Table 16.1 for the FiO_2 achieved by various devices.

Oxygen hood Oxygen hood is a common method of administering oxygen to neonates and infants. Most hoods need a flow of around 7 lit/min.[5] The FiO_2 achieved inside the hood varies from 22 to 90 per cent and depends on the flow rate of oxygen, babies' respiratory needs, the shape of the hood and the size of the side port openings. When high flows are used, a layering effect may occur, with the highest oxygen concentrations settling towards the bottom, for this reason oxygen analyzer sensor should be placed as near to the face of the baby as possible. It is important to maintain adequate heat and humidity inside the hood. Oxygen hoods can be fed through a venturi system so that the FiO_2 inside remains fixed. There is some concern about the noise level inside the hood and the issue is not settled yet.

An Air-entrainment Mask/Venturi Mask

Venturi valves were designed by Campbell in 1960 and are available for 24 to 60 per cent oxygen concentrations. This is the best and economical

Table 16.1: Determining oxygen percentages by various devices

	Liters	Nasal cannula	Simple mask	Partial rebreather mask	Non-rebreather mask
	2	23% to 28%	Not applicable	Not applicable	Not applicable
	3	28% to 30%	— do—	— do—	— do—
	4	Not applicable	— do—	— do—	— do—
Oxygen delivery rate liters/min	5	— do—	40%	— do—	— do—
	6	— do—	45% to 50%	35%	55% to 60%
	8	— do—	Not applicable	45% to 50%	60% to 80%
	10	— do—	— do—	60%	80% to 90%
	12	— do—	— do—	60%	90%
	15	— do—	— do—	60%	90%

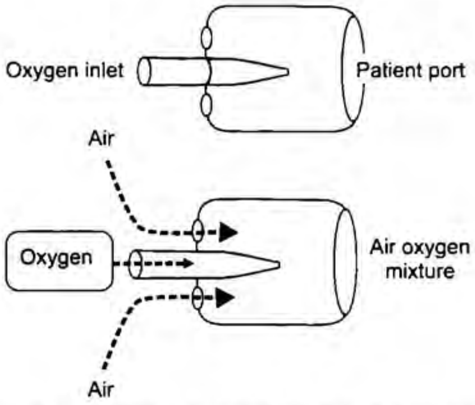

Fig. 16.4: Venturi principle for air entrainment

solution to the problem of oxygenation and most of our patients need to be on this high flow device for their oxygen needs. Oxygen flows through the narrowed orifice creating a jet effect. Air is entrained through the side ports where it blends with the oxygen, delivering the correct concentration of air-oxygen mixture to the mask (Fig. 16.4). Venturi masks may not require humidification because Venturi entrains a much greater flow of room air compared to the oxygen resulting in the delivery of essentially room air humidity.[6] Most patients need air oxygen mixture for correcting hypoxia and not 100 per cent oxygen. Venturi valves deliver air oxygen mixture at high flow rates, the ratio of which will not vary at any point of time and thus fixed FiO_2 is delivered to the patient. Where FiO_2 meters are not available, venturi valves give the best option to monitor the patient as far as the need for oxygenation is concerned. If a given child was maintaining good saturation on a venturi valve of 50 per cent FiO_2 and now he accepts a venturi of 40 per cent and still maintains a good saturation, the child is likely to be recovering from the illness. See Table 16.2 for details of various venturi valves.

The Advantages of using a venturi:

1. A high flow device guarantees the delivery of fixed FiO_2.
2. Can be used in patients with hypoxic drive dependent respiration.
3. Helps in monitoring the patient (Whether the patient is improving or otherwise).
4. Warning signal (patient needing 60% FiO_2 may need ventilatory support).
5. Humidification may not be necessary.
6. Economical and reliable

CPAP (Continuous positive airway pressure)

Indicated as a possible device for correcting Hypoxemia in patients with PaO_2 less than 60 mmHg or FiO_2 of 60 per cent with normal ventilatory activity (Normal $PaCO_2$). Full discussion on CPAP is beyond the scope of this artitle

Table 16.2: Venturi mask: flows and entrainment ratios

Oxygen conc	Total (LMP)	Oxygen flow rate (LMP)	Approx. Air: Oxygen ratio
24%	53	2	25:1
28%	45	4	10:1
31%	47	6	7:1
35%	45	8	5:1
40%	33	8	3:1
50%	32	12	5:3
60%	30	15	1:1

CPAP improves oxygenation by:

1. Increasing the FRC of lungs and thus reducing the work of breathing.
2. Increasing static compliance of lung.[7,8]
3. Recruiting the alveoli for airway exchange.
4. Improving ventilation perfusion relationship.

CPAP or PEEP (Intubated patient) partially obstructs exhalation and thus keep the lungs expanded during expiration (Prevents the total collapse of lung at the end of expiration). It is easy to expand a partially collapsed lung than a lung, which is completely collapsed. Especially in early infancy and in neonates there is a natural tendency of lungs to collapse and hence the benefit of CPAP (Fig. 16.5).

CPAP can be given:

1. Without Intubation
   a. Nasal prongs
   b. Nasopharyngeal catheters.
   c. Tightly fitting mask
2. With Intubation
   a. With ventilator
   b. Without ventilator

Patients on CPAP need to be observed closely as patients on ventilators and especially for:

1. Air leak syndrome
2. Ventilatory failure
3. Decrease in peripheral circulation
4. Sudden loss of CPAP.
5. Respiratory drive.

CPAP can be delivered by various means. These devices partially obstruct the expiratory flow and thus prevent the complete collapse of lung at the end of expiration. Simple device can be made from a bottle with a glass tube immersed in it for the intended depth to deliver the desired CPAP.

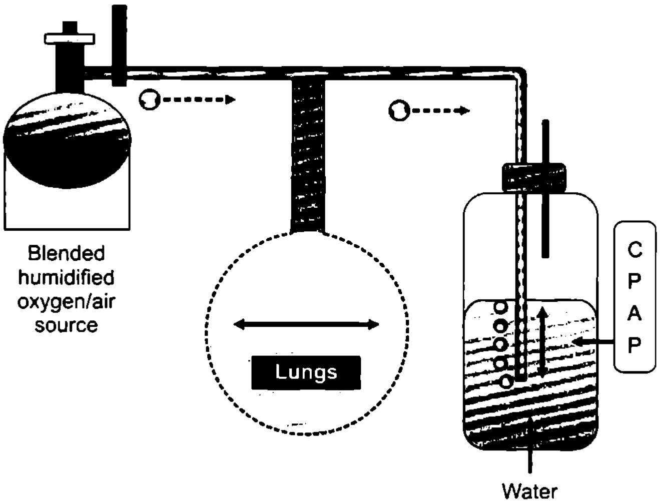

Fig. 16.5: Schematic diagram of CPAP delivery system (CPAP: continuous positive airway pressure)

Patient is weaned from CPAP at a point when he maintains adequate saturation on FiO_2 of 30 per cent. First the CPAP is reduced slowly and then the reduction in FiO_2 follows.

Oxygen concentrator Oxygen concentrator separates the oxygen from the nitrogen in the air by a method using absorption and desorption. Air from the environment passes through the compressor and then through the zeolite, a material that under high pressure absorbs nitrogen. Oxygen on the contrary passes straight through this material.

The outlet pressure of the concentrator is only 5 PSI as compared to the outlet pressure of standard oxygen cylinder, which is 50 PSI. The low output pressure of the concentrator means that the FiO_2 delivered by the concentrator though states a value of 90 per cent, in comparison to the standard oxygen cylinder output, the value would not be more than 40 per cent. Even 40 per cent. FiO_2 is good enough in most situations.

The Principles of Oxygenation

The goal of oxygenation is the consumption of oxygen by the tissues, and to that effect there is no single parameter which can be totally relied upon. Complete assessment of a patient including the clinical examination, pulse oxymetric saturation, blood gases, temporal change in the status of blood gases, gastric tonometry and evidence of anaerobic metabolism are some of the parameters on which the status of oxygenation is assessed. To achieve the optimum level of oxygen in the blood with a minimum possible FiO_2 is the essence of proper oxygenation. Feedback loop for changing FiO_2, adding CPAP or initiating ventilation comes from the data obtained from clinical examination, blood gas values and pulse oxymetric saturation (Fig. 16.6).

Initiation

Initiation of oxygenation should be done without wasting time and with a thought that one can always withdraw oxygen when the need is not felt. Starting FiO_2 should be high in most of the situations but need not be 100 per cent. It is preferable to start

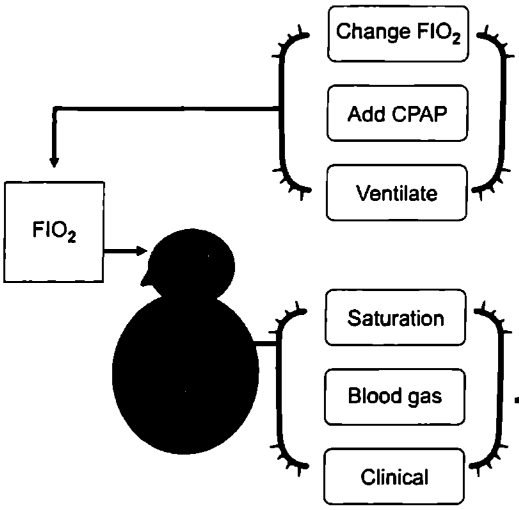
Change FIO$_2$
Add CPAP
Ventilate
FIO$_2$
Saturation
Blood gas
Clinical

Fig. 16.6: Feed back loop for FIO$_2$ change institution of CPAP and ventilation

with FiO$_2$ of 40 to 60 per cent, using a high flow device.

In most of the situations one need not use 100 per cent oxygen, it is indicated only for the following two situations.

1. Resuscitation
2. Transport

Maintenance

Once the patient is stabilized, maintenance therapy is instituted depending on the following principles:

1. Patient should be on high flow system till the time he is in stable cardiorespiratory state.
2. Minimum FiO$_2$ should be used to maintain the saturation of 92 per cent and above.
3. No single investigation or monitoring modality is confirmatory of hypoxia
4. Avoid fluctuations in FiO$_2$.
5. Patient should be nursed in a comfortable environment. The position of patient should ensure patency of airways.
   - Lateral nursing
   - Patient who is looking towards heaven is likely to go there
6. Rarely one needs 100 per cent Oxygen, if required it should never be denied for the fear of toxicity.
7. Close monitoring of all patients is mandatory. It is desirable to use continuous pulse oxymetry.
8. Withdrawal of oxygen support is a decision based on laboratory parameters and clinical situations. It is desirable to consider weaning for patients who are stable with FiO$_2$ of 30 per cent.
9. New-born babies need closer monitoring for hyperoxia. High-risk babies need to have their saturation maintained between 90 to 94 per cent.

Algorithm shown in Figure 16.7 is an excellent guide for an ideal setup with facilities for blood gas and FiO$_2$ monitoring.[8] These facilities are often not available, and hence an alternative strategy is suggested knowing fully well the limitations involved, please see Figure 16.8.

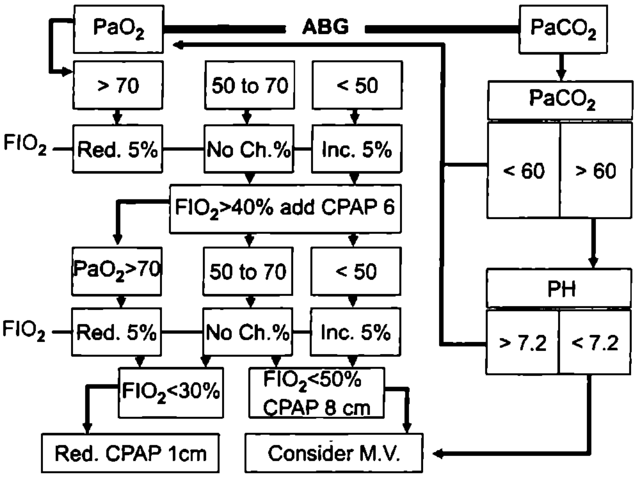
PaO$_2$
ABG
PaCO$_2$
> 70
50 to 70
< 50
PaCO$_2$
FIO$_2$
Red. 5%
No Ch.%
Inc. 5%
< 60
> 60
FIO$_2$>40% add CPAP 6
PaO$_2$>70
50 to 70
< 50
PH
FIO$_2$
Red. 5%
No Ch.%
Inc. 5%
> 7.2
< 7.2
FIO$_2$<30%
FIO$_2$<50% CPAP 8 cm
Red. CPAP 1cm
Consider M.V.

Fig. 16.7: Algorithm for manipulation of FIO$_2$, use of CPAP (continuous positive airway pressure) and MV (mechanical ventilation)

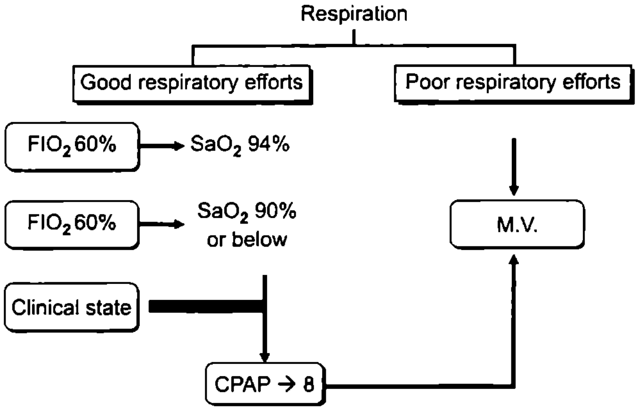
Respiration
Good respiratory efforts
Poor respiratory efforts
FIO$_2$ 60%
SaO$_2$ 94%
FIO$_2$ 60%
SaO$_2$ 90% or below
M.V.
Clinical state
CPAP → 8

Fig. 16.8: Simple clinical algorithm for respiratory support. CPAP (continuous positive airway pressure) and MV (mechanical ventilation)

Patients who are not in a position to maintain adequate oxygenation on FiO_2 of 60 per cent with CPAP of 8 cm of water, are potential candidates for mechanical ventilation. Indications for mechanical ventilation are based on laboratory parameters and clinical condition of the patient.

Oxygen Toxicity

The risk of oxygen toxicity is well documented and can be broadly classified in two categories:

A. Related to high FiO_2

B. Related to high PaO_2

The most important complications are:

1. Retinopathy of prematurity
2. Hypoventilation
3. Absorption atelectasis
4. Bronchopulmonary dysplasia.

What PaO_2 and FiO_2 is Safe?

It is currently estimated that 20 per cent of all infants weighing less than 1500 gm develop evidence of retinopathy.[10] Thus it is advisable to keep the SpO_2 of high-risk babies between 90 to 94 per cent. The most important aspect in the management of ROP is early screening of these babies. American Academy of Pediatrics recommends screening of infants less than 36 weeks gestation, those babies weighing less than 2000 gm and received oxygen and infants less than 1000 gm at birth even if they have not received oxygen.[9-11]

An infant who requires oxygen at 1 week of age but is still oxygen dependent at 28 days of age is defined as having BPD. BPD develops in 15 to 38 per cent of all infants weighing less than 1500 gm who received mechanical ventilation.[12,13]

It is preferable to use as less FiO_2 as possible and for a short period to maintain adequate oxygenation. FiO_2 above 60 per cent is known to be toxic. In patients with chronic lung disease, there is a danger of oxygen induced hypoventilation and in these patients it is desirable to use controlled oxygenation with venturi valves. One must at the same time remember that in life saving situation no amount of oxygen is considered undesirable.

CONCLUSION

Oxygen is a life saving drug. As there are no stores for oxygen, the rapidity with which the treatment is instituted is an important factor that determines the overall prognosis of a patient. As with any other drug there are side effects of oxygen but it should never be withheld for the fear of toxicity. Patients on oxygen need close monitoring similar to patients on ventilators. Optimum oxygenation is the best, hyperoxia is bad, but hypoxia is worst.

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CHAPTER

Blood Gas and Acid-Base Interpretation

Riccardo Munoz, Praveen Khilnani

Normal pH range of Serum is 7.35-7.45. Low pH means high serum H+ concentration. Low pH in serum (acidemia) is caused by acidosis. Acidosis is a process, if untreated leads to acidemia. High pH (alkalemia) is caused by alkalosis. Thus, acidosis and alkalosis are processes and the terms acidemia and alkalemia describe the state of blood.

ACIDOSIS

Acidosis is defined as serum pH value < 7.34.

Acidosis may be caused by increased arterial partial pressure of CO_2 ($PaCO_2$) (respiratory acidosis),[1] by excess of hydrogen ions by anaerobic metabolism (lactic acidosis), exogenous source (methyl alcohol, ethylene glycol, paraldehyde, and salicylic acid) or excessive bicarbonate loss via kidney or gastrointestinal (GI) tract indirectly causing relative excess of H^+ ions (metabolic acidosis).

Natural compensation of respiratory acidosis is attained by retention of HCO_3 (bicarbonate) by the kidneys in an attempt to normalize the pH. Metabolic acidosis is compensated by hyperventilation to lower $PaCO_2$ and thus, to increase the serum pH. Primary or compensated metabolic acidosis can always be recognized by the pH being low as the compensation process does not bring the pH to completely normal value.

ALKALOSIS

Alkalosis is defined as serum pH greater than 7.45. Excessive bicarbonate administration/reabsorption at renal tubules or loss of H^+ ions via renal or GI tract leads to metabolic alkalosis. Increased pH resulting from low $PaCO_2$ constitutes respiratory alkalosis. Natural compensation of metabolic alkalosis is achieved by hypoventilation and CO_2 retention. Respiratory alkalosis is compensated by increased bicarbonate loss at the renal tubular level.

Respiratory acid base disorders are usually simple, i.e. either respiratory alkalosis or respiratory acidosis can exist at one time. Metabolic acid-base disturbances are more complex and can coexist at the same time.

BUFFERING SYSTEM

A buffer is a substance that reduces the change in concentration of free H^+ in a solution to which an acid or base has been added. Thus, for example, more hydrogen ion must be added to a buffered solution to result in a given increase in H^+ than would be required if the solution had no buffer. In a typical patient, there are 30 mEq/L of buffer bases available to buffer hydrogen ions, 75 per cent of which is bicarbonate (normal serum concentration of 23 mEq/L).

HOMEOSTASIS

Homeostasis pertains to maintenance of normal biochemical and physiological parameters. In the adult, there is a normal production and excretion of 24,000 nM/day of CO_2. There is also a turnover of hydrogen of 69 meq/day. Thus, there is constant ongoing acid-base processing: CO_2 is exhaled, and bicarbonate is generated or excreted by the kidney, as necessary. Despite the existence of approximately 105 mEq of hydrogen in the body, there is only 0.0021 mEq of free H^+ in body fluids. The remainder is buffered.

PATHOPHYSIOLOGY

If acidosis occurs, hydrogen ion is buffered; some of the base is lost and a base deficit appears.The maximum possible base deficit is 30. The base must be regenerated to a normal level. The addition of H^+ to the system generates CO_2 and the respiratory rate increases by stimulation of the respiratory center in medulla. The lungs expire the CO_2 and thus affect pH through the Henderson-Hasselbalch relationship:

$$pH = 6.1 + \log \frac{HCO_3}{0.03 \times pCO_2}$$

OR

$$pH = pK \log \frac{\text{bicarbonate}}{\text{carbonic acid}}$$

In this equation pK is the dissociation constant of the carbonic acid (pK = 6.1). Note, however, that although pH is affected, no net loss of H+ occurs. In other words, the respiratory system affects pH through modifications of the major body buffer system (carbonic acid) but can neither excrete H^+ nor regenerate HCO_3. The kidneys control the hydrogen ion and bicarbonate concentrations by regulating bicarbonate reabsorption and by new bicarbonate generation. In addition, the kidneys synthesize ammonia in response to systemic acidosis.

METABOLIC ACIDOSIS (FLOW CHART 17.1)

Metabolic acidosis is a common finding in the pediatric intensive care unit (Table 17.1).

If bicarbonate loss is the cause (e.g. diarrhea with HCO_3 loss, or dilutional acidosis in which bicarbonate is diluted from infusion of nonbicarbonate containing solutions), or if a precursor to hydrochloric acid (e.g. ammonium chloride) is added to the system (rare), the chloride will proportionately increase and the anion gap (major cations minus major anions) will be normal.

Conversely, an increase in unmeasured cations will cause an increase in the anion gap. This can be caused by an accumulation of lactic acid, other organic acids, and exogenous acids (ethylene glycol, methanol, paraldehyde, and salicylic acid).

Table 17.1: Etiology of metabolic acidosis

(Anion gap = Major cations in blood – Major anions in blood)

$(Na^+ K^+ - HCO_3^- + Cl^-)$

1. Normal anion gap acidosis
   a. Diarrhea Small bowel, biliary, or pancreatic tube or fistula drainage. Ureteral diversion with bowel (uretero sigmoidostomy, ileal conduit). Bowel augmentation, cystoplasty
   b. Exogenous chloride containing compounds $CaCI_2$, $MgCl_2$. NH_4CI, HCI, cholestyramine, arginine HCI parenteral alimentation acidosis
   c. Renal tubular acidosis
   d. Carbonic anhydrase inhibitors acetazolamide, mafenide
   e. Mineralocorticoid deficiency
   f. Dilution (rapid extracellular fluid expansion)
2. Increased anion gap acidosis (normochloremic)
   a. Ketoacidosis: Diabetes mellitus, starvation, glycogen storage disease (type 1), inborn errors of amino acid, or organic acid metabolism
   b. Lactic acidosis: Tissue hypoxia, inborn errors of carbohydrate pyruvate metabolism
   c. Exogenous toxins: Salicylates, methanol, ethylene glycol, paraldehyde
   d. Chronic renal failure

Effects of Metabolic Acidosis

Metabolic acidemia causes decreased myocardial contractility, decreased peripheral resistance, decreased adrenergic-receptor sensitivity, and predisposes to myocardial irritability. It also tends to cause a shift of potassium to extracellular space (hyperkalemia). Clinically a patient with primary metabolic acidosis is seen with cool extremities, hypotension, lethargy and hyperventilation (to compensate by blowing off CO_2 by lungs and bring the pH to as normal as possible). Expected $PaCO_2$ is determined by the following equation:

$$PaCO_2 = (1.5 \times HCO_3) + 8 \pm 2 \ (1)$$

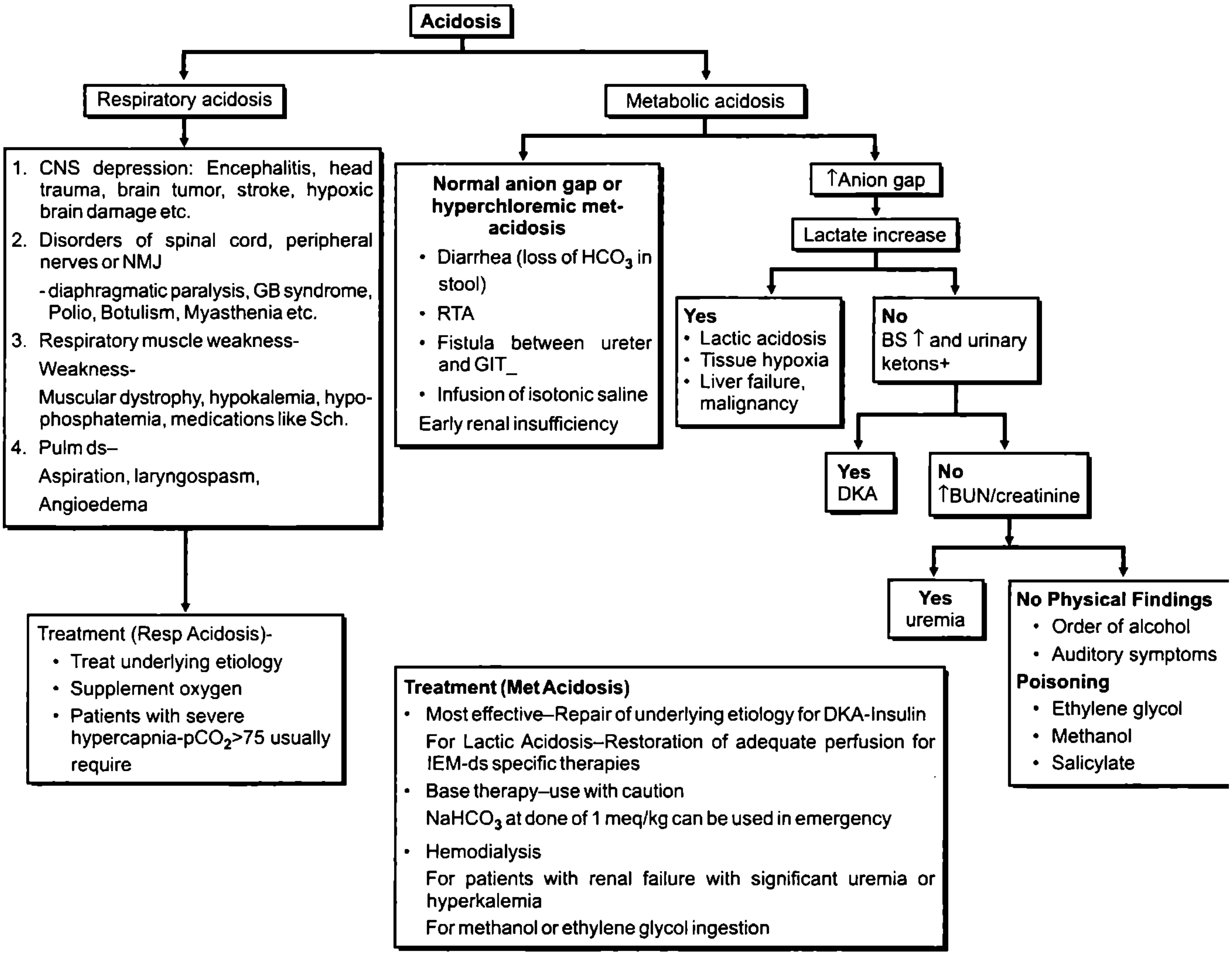
Values outside this range indicate a mixed disorder.

TREATMENT

Much attention has been paid to the treatment of metabolic acidosis.

A. *Treatment of the underlying cause* is most important, for example, treatment of hypovolemia, shock, poor cardiac output will usually correct acidosis due to above causes.

Flow chart 17.1: Approach to child with acidosis


Acidosis
Respiratory acidosis
Metabolic acidosis
1. CNS depression: Encephalitis, head trauma, brain tumor, stroke, hypoxic brain damage etc.
2. Disorders of spinal cord, peripheral nerves or NMJ
- diaphragmatic paralysis, GB syndrome, Polio, Botulism, Myasthenia etc.
3. Respiratory muscle weakness-
Weakness-
Muscular dystrophy, hypokalemia, hypophosphatemia, medications like Sch.
4. Pulm ds–
Aspiration, laryngospasm,
Angioedema
Treatment (Resp Acidosis)-
• Treat underlying etiology
• Supplement oxygen
• Patients with severe hypercapnia-pCO$_2$>75 usually require
Normal anion gap or hyperchloremic met-acidosis
• Diarrhea (loss of HCO$_3$ in stool)
• RTA
• Fistula between ureter and GIT_
• Infusion of isotonic saline
Early renal insufficiency
↑Anion gap
Lactate increase
Yes
• Lactic acidosis
• Tissue hypoxia
• Liver failure, malignancy
No
BS ↑ and urinary ketons+
Yes
DKA
No
↑BUN/creatinine
Yes
uremia
No Physical Findings
• Order of alcohol
• Auditory symptoms
Poisoning
• Ethylene glycol
• Methanol
• Salicylate
Treatment (Met Acidosis)
• Most effective–Repair of underlying etiology for DKA-Insulin
For Lactic Acidosis–Restoration of adequate perfusion for IEM-ds specific therapies
• Base therapy–use with caution
NaHCO$_3$ at done of 1 meq/kg can be used in emergency
• Hemodialysis
For patients with renal failure with significant uremia or hyperkalemia
For methanol or ethylene glycol ingestion

B. *Alkalinization* of the body with bicarbonate ions has long been practiced. The intent of such therapy is to reverse the acidemia to allow a return to more normal organ function.This therapy has been criticized for a number of reasons such as a lack of data showing efficacy, worsened blood pressure and cardiac output in certain experimental situations following administration of bicarbonate and use of a systemic base reduces H^+ concentration exrtra cellularly by generating CO_2. This CO_2 readily moves intracellulary and thus worsens intracellular acidosis.The sodium and osmotic load have also been of concern.

Despite these reservations, bicarbonate therapy is still used cautiously in the patient with severe metabolic acidosis while treatment of the primary cause is on going. The dose of bicarbonate is 1 mEq/kg body weight intravenously repeated as needed. When the arterial blood gas (ABG) data is available, the dose of sodium bicarbonate (meq) is calculated by the formula:

$$0.3 \times \text{wt. in kg} \times \text{base deficit}$$

Pushes of bicarbonate should be avoided due to danger of bradycardia or sudden hypotension. In premature neonates, use of sodium bicarbonate used as intravenous bolus has been associated with increased incidence of intra ventricular hemorrhage due to high osmolarity.

An alternative drug to bicarbonate is trishydroxymethylaminomethane (THAM). Infusion of

THAM consumes CO_2, does not have the sodium load, and may penetrate intracellularly more readily. It can cause respiratory depression, hyperkalemia, and hypoglycemia. Dose is 1 mEq/kg given intravenously.

METABOLIC ALKALOSIS (pH > 7.44 BLOOD BICARBONATE > 26 mEq/L) (FLOW CHART 17.2)

Metabolic alkalosis (Table 17.2) in the PICU is most commonly due to iatrogenic fluid depletion resulting in concentration of HCO_3 (concentration alkalosis), increased tubular reabsorption of HCO_3 due to chloride depletion, and loss of potassium thus obligating H^+ loss in the urine (example, furosemide therapy). It may also be found as the result of a loss of gastric secretions. Compensatory respiratory acidosis tries to lower the pH to normal. A rise in the pCO_2 can be predicted by the following equation:

$$\text{Expired } pCO_2 = 0.9 \times HCO_3 + 9 \pm 2$$[2]

A value of pCO_2 outside this range is indicativ of a superimposed respiratory disorder or additiona acid base abnormality.

Table 17.2: Etiology of metabolic alkalosis

Generation of metabolic alkalosis:

A. Loss of H^+ ions
  i. Gastrointestinal
    a. Vomiting
    b. Nasogastric aspiration
    c. Congenital chloride wasting diarrhea
  ii. Renal
    a. Diuretics (thiazides, furosemide, ethacrynic acid)
    b. Excess mineralocorticoid activity
      - Endogenous (hyperaldosteronism, Cushing's disease, adrenogenital syndrome)
      - Exogenous (steroid therapy, licorice, chewing tobacco)
    c. Bartter's syndrome
      - Chloride deficient infant formula
      - Post hypercapnia

B. Gain of HCO_3
  i. Exogenous alkali (HCO_3, citrate, acetate, lactate administration)

C. Contraction of extracelular volume
  i. Chronic diuretic therapy
  ii. Cystic fibrosis (infants)

Maintenance of metabolic alkalosis:

A. Renal failure
B. Extracellular Volume depletion
C. Increased mineralocorticoid
D. Potassium depletion
E. Chloride depletion

Treatment

The treatment of metabolic alkalosis is to correc potassium deficiency and restore fluid volume a appropriate. In patients with metabolic alkalosis du to vomiting or diuretic therapy. Treatment witl normal potassium chloride usually corrects th alkalosis (Saline responsive alkalosis). If salin therapy does not correct it, mineralocorticoid level may be high as discussed earlier. Use of spironolactone is indicated. In patients with renal arter stenosis angiotensin converting enzyme (ACE inhibitors (captopril) therapy may be indicated Patients with Bartters syndrome respond t prostaglandin inhibitors such as Indomethacin (Salin unresponsive alkalosis).[3]

Alternatively, carbonic anhydrase inhibitor (acetazolamide) may be used. For severe case (myocardial depression assumed to be due t severe metabolic alkalemia), 0.1 normal hydrochloric acid may be used intravenously (rarel required).

RESPIRATORY ACIDOSIS (pH < 7.35 WITH PRIMARY $PaCO_2$ > 45 mmHg)

Respiratory acidosis is characterized by blood ga pH less than 7.35 and a primary increase in PaCO (> 45 mmHg) owing to ineffective alveolar ventilation. Common causes are listed in Table 17.3. A acute increase in pCO_2 is buffered by titration o nonbicarbonate intracellular buffers withou significant renal compensation for 12 to 24 hours The serum HCO_3 concentration rarely rises abov 32 mEq per liter during that time. If the serum HCO is greater than 32 mEq per liter, a mixed respirator acidosis and metabolic alkalosis disorder is likely t occure. With chronic respiratory acidosis (duratio greater than 3 days) and metabolic compensatio by the kidneys, serum HCO_3 concentration increase further, but rarely exceeds 45 mEq per liter.

Treatment is to improve ventilation by treatmen of primary cause (See Chapters on Mechanica Ventilation, Non-invasive Ventilation, and Tracheostomy).

Flow chart 17.2: Approach to patient with alkalosis

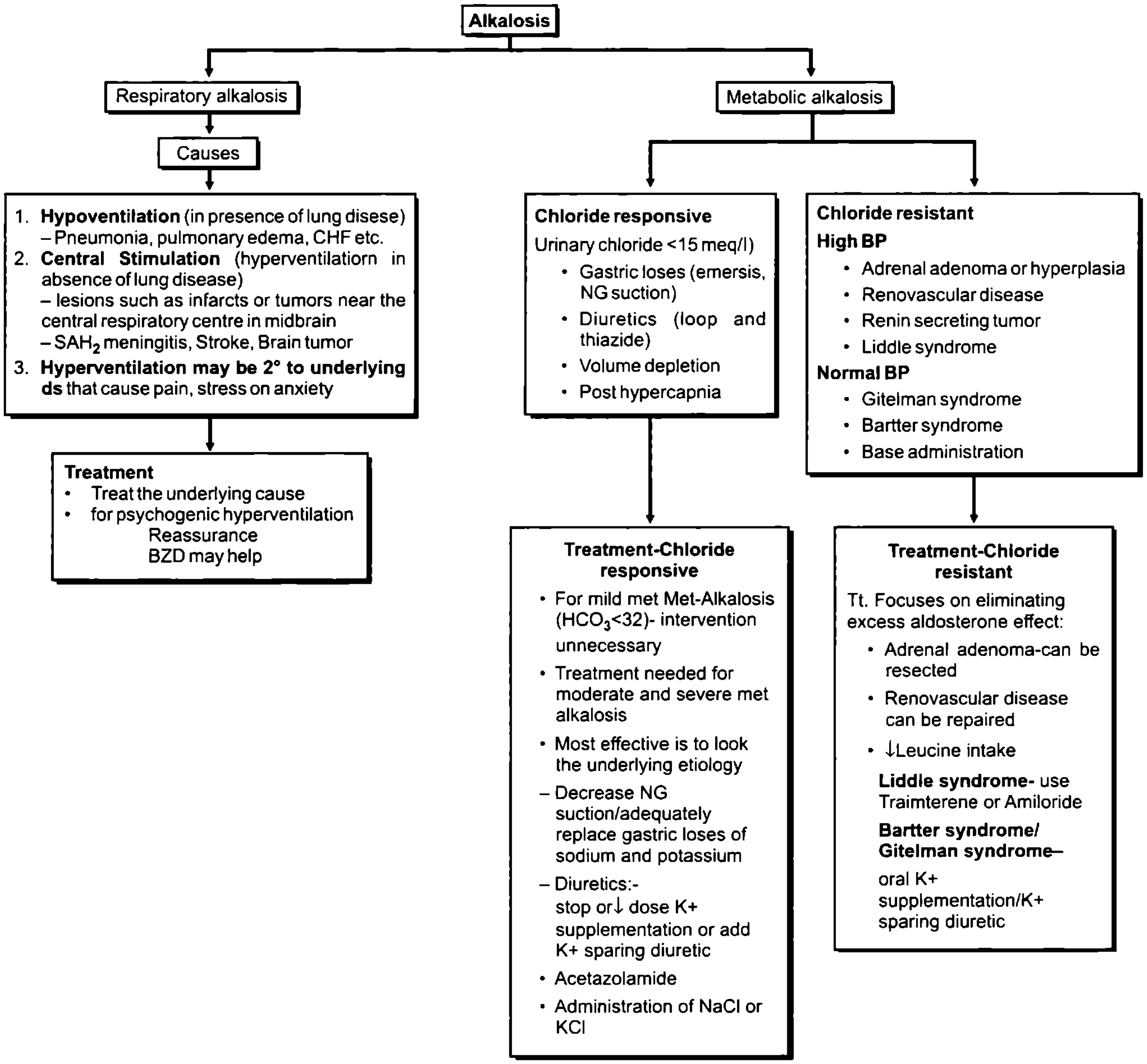

Alkalosis
Respiratory alkalosis
Causes
1. Hypoventilation (in presence of lung disese) – Pneumonia, pulmonary edema, CHF etc.
2. Central Stimulation (hyperventilatiorn in absence of lung disease)
– lesions such as infarcts or tumors near the central respiratory centre in midbrain
– SAH₂ meningitis, Stroke, Brain tumor
3. Hyperventilation may be 2° to underlying ds that cause pain, stress on anxiety
Treatment
• Treat the underlying cause
• for psychogenic hyperventilation
Reassurance
BZD may help
Metabolic alkalosis
Chloride responsive
Urinary chloride <15 meq/l)
• Gastric loses (emersis, NG suction)
• Diuretics (loop and thiazide)
• Volume depletion
• Post hypercapnia
Chloride resistant
High BP
• Adrenal adenoma or hyperplasia
• Renovascular disease
• Renin secreting tumor
• Liddle syndrome
Normal BP
• Gitelman syndrome
• Bartter syndrome
• Base administration
Treatment-Chloride responsive
• For mild met Met-Alkalosis (HCO₃<32)- intervention unnecessary
• Treatment needed for moderate and severe met alkalosis
• Most effective is to look the underlying etiology
– Decrease NG suction/adequately replace gastric loses of sodium and potassium
– Diuretics:- stop or↓ dose K+ supplementation or add K+ sparing diuretic
• Acetazolamide
• Administration of NaCl or KCl
Treatment-Chloride resistant
Tt. Focuses on eliminating excess aldosterone effect:
• Adrenal adenoma-can be resected
• Renovascular disease can be repaired
• ↓Leucine intake
Liddle syndrome- use Traimterene or Amiloride
Bartter syndrome/ Gitelman syndrome– oral K+ supplementation/K+ sparing diuretic

Table 17.3: Causes of respiratory acidosis

Acute and chronic lung disease
- Acute airway obstruction (croup, epiglottitis, foreignbody aspiration)
- Bronchospasm (asthma, bronchiolitis)
- Chronic obstructive lung disease (cystic fibrosis, bronchopulmonary dysplasia)
- Interstitial lung disease
- Pneumonia
- Pulmonary edema
- Impaired lung motion
- Pleural effusion
- Pneumothorax

Contd...

Contd...

Thoracic cage abnormalities
- Flailchest,
- Scoliosis,
- Osteogenesis imperfecta

Neuromuscular disorders
- Brainstem or spinal cord injury or tumor
- Guillain-Barre syndrome
- Poliomyelitis
- Myasthenia gravis
- Muscular dystrophy
- Botulism
- Central nervous system depressant
- Drugs (narcotics, sedatives, tranquilizers)
- Pickwickian syndrome (Central hypoventilation syndrome)

RESPIRATORY ALKALOSIS (PRIMARY DECREASE IN $PaCO_2 < 35$ mmHg AND pH > 7.44)

A primary decrease in $PaCO_2$ and arterial blood gas pH greater than 7.44 results in respiratory alkalosis. Respiratory alkalosis is probably the most common acid- base disorder among seriously ill patients. The cause is hyperventilation from a variety of sources (Table 17.4). Acutely, the patient may have obvious rapid breathing. When respiratory alkalosis becomes chronic, the respiratory rate may be almost normal with deeper breaths. The initial fall in $PaCO_2$ is acutely titrated by intracellular buffers. Within 1 to 2 days, renal compensation allows the blood gas pH to returns toward normal. Metabolic compensation actually returns the extracellular pH to normal in high dwellers and some persons with respiratory alkalosis of longer than two weeks' duration. Increased production of tissue lactic acid was considered potentially important in this process, but measured increases in blood lactate levels have been only 0.5 to 1.0 mEq per liter, an insufficient rise to be significant in normalizing pH.

Treatment involves treatment of the primary cause, treatment of the underlying pain or anxiety state.

Table 17.4: Causes of hyperventilation and respiratory alkalosis

- Anxiety
- Central nervous system disorders (trauma, vascular accident tumor, infection)
- Fever, Sepsis
- High altitude
- Pneumonia
- Pulmonary embolism
- Congestive heart failure with hypoxemia
- Mechanical ventilation
- Salicylates
- Liver failure
- Hyperthyroidism

Practical Tips to Approach Acid-Base Disorders

The following questions must be answered before one decides to treat the acid-base disorder:

a. Is this a respiratory or metabolic disorder?
b. Is this a simple or mixed disorder?
c. Is this an acute or chronic disturbance?

a. A respiratory disorder is a primary change in PCO_2 concentration, whereas a metabolic disorder is a primary change in bicarbonate concentration.
b. The simple acid-base disturbance is defined by a primary change in one parameter (PCO_2, or HCO_3). The pH indicates if the disorder is a primary acidosis or primary alkalosis. A mixed acid-base disorder is defined as the coexistence of more than one acid base disorder.
c. An acute disturbance is measured in minutes to hours, but a chronic process lasts days to weeks or longer.[4]

A primary respiratory disorder should be considered if the pH and pCO_2 change in opposite directions. The altered relationship between the magnitude of change in pCO_2 relative to the change in pH indicates the presence of a concomitant metabolic disorder, or an incomplete compensatory response.

The pH changes 0.008 units for every 1 mmHg change in acute uncompensated acidosis. pH changes only 0.003 units for every 1 mmHg change in pCO_2 in the presence of chronic compensated acidosis.

In the presence of partially compensated respiratory acidosis, the pH changes between 0.003 to 0.008 for every 1 mmHg change in pCO_2 (Table 17.5).[5]

Table 17.5: Respiratory acidosis interpretation

pH change (below normal)	*pCO_2 change (above normal)*	*Diagnosis*
> 0.008	1 mm Hg	Associated metabolic acidosis
0.003 to 0.008	1 mm Hg	Partially compensated respiratory acidosis.
< 0.003	1 mm Hg	Associated metabolic alkalosis

Modified from Marino P: Algorithms for acid-base interpretations. In: The ICU Book. Marino P (Ed): Malvern, Lea & Febiger, 1991;415.

Regardless of the respiratory acidosis being uncompensated or partially compensated, if the pH is below normal and the pCO_2 is elevated, the primary disorder is respiratory acidosis.

During acute uncompensated respratory alkalosis, the serum pH increases 0.008 units for every

Table 17.6: Interpretation of respiratory alkalosis

pH change (above normal)	*pCO$_2$ change (below normal)*	*Diagnosis*
> 0.008	1 mm Hg	Associated metabolic alkalosis.
0.002-0.008	1 mm Hg	Partially compensated respiratory alkalosis.
< 0.002	1 mm Hg	Associated metabolic acidosis.

Modified from Marino P: Algorithms for acid-base interpretations. In: The ICU Book. Marino P (Ed.): Malvem. Lea & Febiger, 1991,415.

1 mmHg decrease in pCO$_2$. However, during chronic compensated respiratory alkalosis, the serum pH increases only 0.002 units for every 1 mmHg decrease in pCO$_2$ (Table 17.6).

MIXED ACID-BASE DISORDERS

A mixed acid-base disorder is defined as the coexistence of more than one acid-base disorder.

Mixed Metabolic and Respiratory Acidosis

Plasma bicarbonate concentration is low and pCO$_2$ value is high. Because of the coexistence of these two acidotic disorders, the pH value is significantly decreased. Common examples of mixed metabolic and respiratory acidosis are cardiopulmonary arrest, adult respiratory distress syndrome and septic shock, asthma and lactic acidosis due to increased work of breathing.

Mixed Metabolic and Respiratory Alkalosis

A mixed metabolic and respiratory alkalosis is defined when the plasma bicarbonate is high and the pCO$_2$ is low.[3] These acid-base disorders may be present in children with respiratory alkalosis associated with congestive heart failure and diuretic therapy.

Mixed Metabolic Alkalosis and Respiratory Acidosis

These disorders show high plasma bicarbonate and excessively high pCO$_2$ (above the normal compensatory mechanism). These acid-base disturbances a commonly seen in patients with bronchopulmonar dysplasia and diuretic therapy. Similarly, patien with chronic respiratory failure and excessive gastri drainage through nasogastric tube, may present wit these disorders.

Metabolic Acidosis and Respiratory Alkalosis

A diagnosis of mixed metabolic acidosis and respiratory alkalosis can be made when both plasma bicarbonate and pCO$_2$ are seriously low (above the norma compensation), and the pH is normal or near normal

This acid-base disorder may be associated wit rapidly corrected metabolic acidosis, salicylat intoxication and in the hepatorenal syndrome.

Treatment

Therapy must be directed to correct the precipitan factors, and, each acid-base disturbance needs specifi therapy. For example, in a dehydrated child wit metabolic acidosis and respiratory acidosis, th therapy must include fluids and bicarbonate to trea the metabolic acidosis, and ventilatory support t correct the respiratory acidosis.

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CHAPTER

Upper Airway Obstruction in Children

I David Todres, Guiseppe Marraro, Praveen Khilnai

Acute upper airway obstruction is a potentially life-threatening condition in the infant or child. The progression of airway obstruction may be rapid, therefore requiring astute recognition and anticipation of the problem. A basic knowledge of the embryological development, anatomy and physiology of the upper and lower airways are important to understand the pathology and management of airway obstruction.

PEDIATRIC AIRWAY

Nose

It has pseudostratified ciliated mucous lining which helps move mucous to bring it outside. Newborn is an obligate nose breather until between two and six months of age. The reason for this is that the epiglottis is very close to the nasopharynx. With growth, the larynx descends caudad and the infant is able to breath by the mouth.

Larynx and Trachea

Fetal larynx is at (cervical vertebra level) C1, C2 and C4. In the infant, larynx is located opposite C3 to C4. Arytenoids are relatively large. Epiglottis remains at a 45 degree angle to the anterior pharyngeal wall and is omega shaped. It is tubular with a narrow base and long. Infant larynx is funnel shaped (Fig. 18.1). The narrowest portion of the infant airway is the area of cricoid ring. The vocal cords are concave and at an angle to the trachea. The trachea is approximately 5 to 7 cm long at birth.

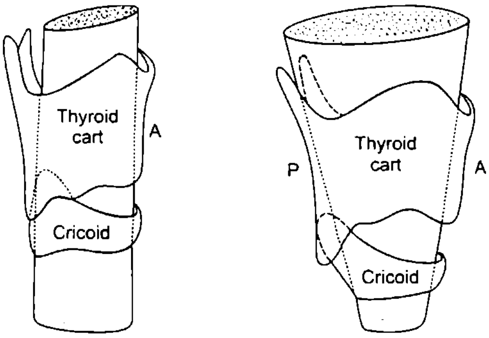


Fig. 18.1: (A) Adult airway (cylindrical) and (B) Infant airway (funnel shaped)

The main bronchi branch from the trachea a approximately equal angles, but as the patient grows the right main stem bronchus is more in line with the trachea. At four to six months of age, the epiglottis loses contact with the soft palate, and the infant is able to breath by mouth. By 12 years o age, the epiglottis and the larynx are in the adul location of C6. The narrowest portion of the adul airway is the glottic opening. The length of the trachea increases to 11 cm in the adult, as opposed to 5 to 6 cm in a one to three month old child. The nasal airway and mouth contribute to half of the total respiratory resistance. The glottis accounts fo approximately 25 per cent of the respiratory resistance. The trachea and bronchi account fo another 15 per cent. Changes in tracheal lumen size with inspiration and expiration as well as with cervical extension and flexion have been noted in newborn infants.

Developmental Anatomy

Respiratory tract develops from the ventral surface of the foregut in the early embryonic period. A definable larynx is seen at 6 weeks gestation and by the 10th and 11th week of gestation, the major structures of the larynx have developed. Failure of the true cords to separate appropriately to form the primitive glottis results in a complete or partial laryngeal web. By 26 weeks of gestation, larynx develops important function of protecting the lower airway and phonation. Protecting the lower airway occurs through neurally controlled closure of the glottis during swallowing. Development of receptors which respond to irritant stimuli by inducing laryngospasm place by 26 weeks of gestation. In the trachea and major bronchi, C-shaped rings of cartilage support the airway structure. Cartilage is present in airways as small as 1 to 2 mm in diameter. It maintains airway patency despite large changes in intrathoracic pressure with the phases of respiration. Developmentally, there are several anatomical differences between the airway of the child and adult. Infants have a cephalad larynx (C3-4 compared to adult larynx C5-6) and a large epiglottis constantly touching the soft palate thereby preventing mouth breathing. By 4-5 months of age as the larynx descends down, epiglottis no longer touches the soft palate thereby allowing mouth breathing. The child's tongue is relatively large for the smaller oral cavity due to buccal fat pads and receded mandible. Increase in size of the tongue (e.g. hemangioma, Down's syndrome, Beckwith Wiedemann syndrome) or markedly receded mandible (Pierre Robin, Treacher Collins syndrome) readily leads to airway obstruction.

In the child, the attachment of the vocal cords is lower at its anterior attachment than posteriorly. In the adult, the vocal are on a horizontal plane occasionally making endotracheal intubation more difficult in the infant as a result of the tube being held up at the anterior commissures of the vocal folds.

The area within the cricoid cartilage, or subglottic region, is the narrowest part of the child's upper airway, as opposed to the rima glottides in the adult. The relatively narrow subglottic area is predisposed to edema from croup or following endotracheal intubation or bronchoscopy. Swelling in this area in the child may cause stridor and respiratory distres An equivalent amount of swelling in the adult woul have minimal effects due to much larger diamete resistance being inversely proportional to the radiu of the lumen of the airway (Fig. 18.2).

Histologically, the mucosa of the mouth i continuous with that of the larynx and trachea. Th mucosa is covered with squamous and pseudostratified ciliated epithelium and is tightly adheren to the vocal cords and tracheal surface of th epiglottis, but loosely adherent elsewhere. Inflammatory changes above the vocal cords are limited b the "barrier" formed by the tightly adherent mucos at the vocal cords. Thus supraglottitis (epiglottitis is usually limited to the supraglottic area. Similarl inflammation in the subglottic region leads t subglottic edema in the loosely adherent mucos below the vocal cords, but does not usually sprea above the level of the vocal cords.

Physiology

In the neonate, the nasal passages account fo 25 per cent of the total resistance to airflow compare to 60 per cent in the adult. Lower airway contribute majority of airway resistance due to relatively smal size of the airways and lack of supportive structures Due to relatively soft-cartilaginous support, th larynx, trachea and bronchi in the infant are considerably more compliant than in the adult. Variou distending and compressive forces have a significan effect on airway caliber. The extrathoracic trache is subject to different stresses than the intrathoraci trachea. With normal inspiration, the negativ pressure developed within the chest is transmitte

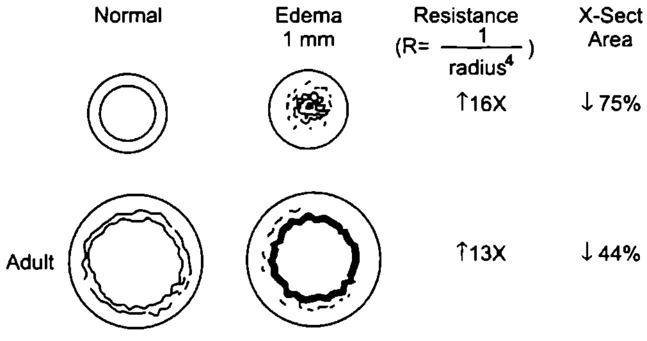


Fig. 18.2: Pediatric airway resistance difference (from adult)

to the large airways including the intrathoracic trachea tending to cause dilation. However, at the thoracic inlet, dynamic compression occurs as a result of the pressure differential between atmospheric pressure and the negative pressure within the extrathoracic trachea. With normal inspiration, this compression is relatively slight and patency of the airway is not compromised. Normal expiration is a passive process driven by the elastic recoil of the lung. Transmural pressures are positive along the entire tracheobronchial tree. There are no significant changes in airway caliber. With obstruction of the extrathoracic airway (e.g. laryngotracheobronchitis, supraglottitis, foreign body), inspiratory effort leads to increased negative pressure within the chest and airway. This leads to a greater difference between ambient pressure and the negative pressure within the extrathoracic trachea. As a result, significant dynamic inspiratory collapse of the extrathoracic trachea will occur, particularly at the thoracic inlet. Intrathoracic airway caliber is only minimally affected because inspiratory pressures within the airways and pleural pressure fall to a similar extent.

The phenomenon of dynamic collapse of the airway has particular relevance in treating acute airway obstruction. Marked transmural pressure changes occur when the infant is agitated and crying. Thus efforts to relieve anxiety and crying are crucial in minimizing dynamic collapse of the airway. In addition, applying continuous positive pressure via a face mask and adjustable pop off valve in the severely obstructed child will counteract dynamic collapses of the airway and facilitate gas exchange.

History and Physical Examination

In evaluating a child with airway obstruction, a history of the illness should not be overlooked. Careful recounting of the onset may suggest foreign body aspiration. Some illnesses progress more slowly (e.g. laryngotracheobronchitis) as opposed to a more sudden and acute onset in a sicker child (e.g. supraglottitis). The time of onset of the illness may suggest a congenital abnormality, that is symptoms starting at birth or shortly after. An infant presenting with "inspiratory stridor" at 1 month of age should not be diagnosed as croup; an alternate diagnosis, e.g. subglottic hemangioma or another condition must be considered.

An initial physical examination involves observing the child to assess how severe the airway obstruction is and whether immediate therapeutic intervention is necessary. Listening to the child provides clues to the approximate location of the obstruction. Impiratory stridor is characteristic of upper airway obstruction (e.g. croup, supraglottitis, vocal cord paralysis) while expiratory stridor has its origin in obstruction of the distal respiratory tract (foreign body, compression from a vascular ring). In severe situations, an inspiratory and expiratory stridor may exist. Signs of acute distress are reflected by an increased respiratory rate, nasal flaring, retractions (suprasternal, sternal, intercostal and subcostal) and cyanosis breathing air. Cyanosis reflects severe hypoxemia. The child may be leaning forward with an open mouth and drooling (e.g. supraglottitis). Drooling of secretions can occur because of an inability to swallow secretions. Dysphagia occurs with supraglottitis and esophageal foreign bodies. The agitated child is one who is hypoxemic. In a critical situation, aggressive therapy (e.g. intubation) to secure a safe and adequate airway may be necessary.

In suspected cases of supraglottis, direct examination of the throat is best avoided as attempts at visualizing the pharynx with a tongue blade may precipitate acute airway obstruction. Pulse oximetry is a good non-invasive measure of oxygen saturation in a child with stridor. Transcutaneous CO_2 monitoring has been shown to correlate with increasing upper airway obstruction in laryngotracheobronchitis.

Special Investigations

Roentgenograms The need for radiographic studies must be carefully evaluated as the manipulations of the procedure must not increase the risk of further airway obstruction. Anterior-posterior and lateral views of the entire airway should be obtained. The procedure should be performed in the upright position as this is usually the most comfortable for the patient. Placing a child with supraglottitis in the supine position may precipitate acute and dangerous airway obstruction. On anterior-posterior view of airway, subglottic narrowing is usually apparent in laryngotracheobronchitis (Fig. 18.3). Severe upper airway obstruction is associated with distension of the hypopharynx. Lateral view of airway may show swollen epiglottis as outline of the posterior part of the tongue is followed inferiorly to the level of epiglottis (Thumb sign) (Fig. 18.4). If epiglottitis is clinically suspected, a normal lateral view of the airway may not be enough to rule it out. A direct visualization in the operating room under general anesthesia is therefore necessary based on clinical suspicion alone (Fig. 18.5).

Chest roentgenogram may also reveal the presence of acute pulmonary edema seen occasionally with severe upper airway obstruction. Pulmonary edema may manifest immediately following relief of airway obstruction with, for example, tracheal intubation. In long-standing upper airway obstruction, hypoxemia and pulmonary hypertension will lead to cardiac failure and evidence of this may be seen on X-ray.

Fluoroscopy and computerized axial tomography may be helpful when standard X-rays are unsatisfactory in defining the site and extent of airway obstruction. A barium swallow may be a helpful procedure in defining compression of the trachea by a vascular ring, e.g. double aortic arch (Fig. 18.6). It is important to keep in mind that stridor is a symptom produced by upper airway obstruction. A cause for stridor therefore must be looked for even if radiological studies including airway flouroscopy and CT scan of the airway are negative.

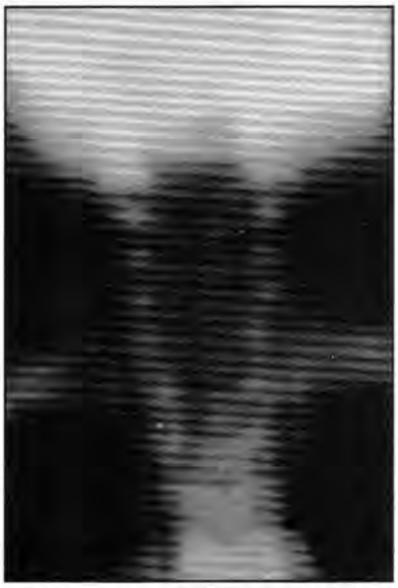


Fig. 18.3: See airway narrowing in laryngotracheobronchitis (CROUP)

Direct examination of the airway by laryngoscopy and bronchoscopy is necessary for making a diagnosis of the site of the obstruction, its extent and the cause. Flexible fiberoptic bronchoscopy is now being routinely used for evaluation of stridor in children. Instruments have been designed which have an outer diameter of 3.5 mm and a 1.2 mm suction channel. An ultrathin fiberoptic bronchoscope with an outer diameter 2.4 mm is now available for airway evaluation of premature and younger infants. In the hands of the experienced physician, it is a safe and

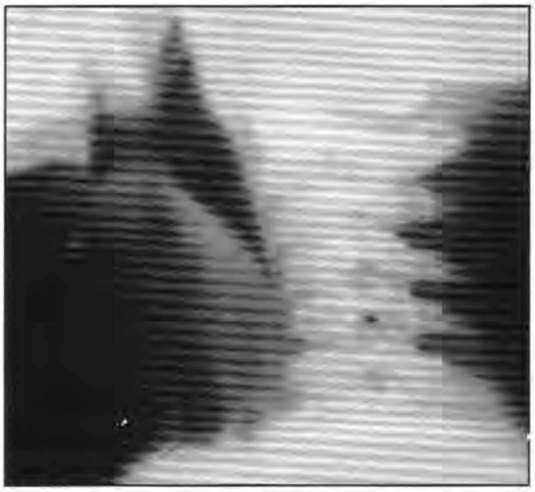


Fig. 18.4: See swollen epiglottis in lateral view of neck airway in patient with epiglottitis (Thumb sign)

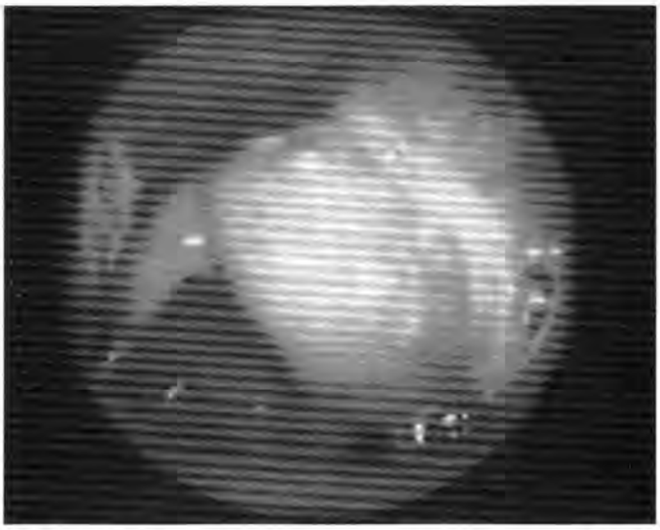


Fig. 18.5: Epiglottitis *(For color version see Plate 6)*

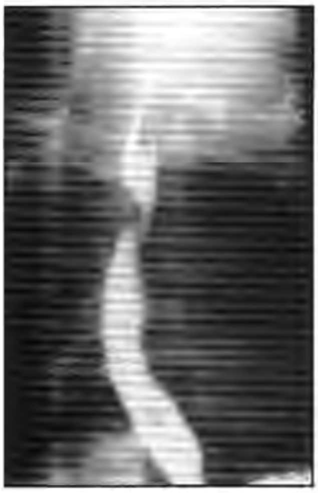


Fig. 18.6: Barium swallow showing narrowing of upper end of esophagus with compression resulting from double aortic arch (vascular ring)

effective instrument for exploring the pediatric airway. Performed under sedation and local anesthesia, it carries less risk than rigid bronchoscopy under general anesthesia. It is particularly advantageous in evaluating the cause of stridor as there is less distortion of the child's airway anatomy; also dynamic airway collapse during respiration is better appreciated than would be the case if the child was under general anesthesia. When rigid bronchoscopy is performed, the procedure must be carried out under appropriate conditions with skilled surgeons and anesthesiologists. The rigid Storz bronchoscope and Hopkins rod lens systems are excellent devices for removal of a foreign body from the airway when compared to fiberoptic bronchoscopes. Passage of fiberoptic bronchoscope through the rigid bronchoscope may be used to visualize smaller airways where rigid bronchoscope is hard to reach. Airway obstruction may also be caused by a foreign body in the esophagus compressing the trachea and require esophagoscopy for its removal.

Physiology Studies

Physiologic studies of airway resistance by measuring inspiratory and expiratory airflow produces flow-volume loops. These are sensitive indicators of airway obstruction when traditional clinical methods are unable to detect an obstruction. They may be diagnostic in identifying the site of ob truction.

SPECIFIC DISEASES

Various causes of upper airway obstruction neonates and older children are listed in Tables 1 and 18.2. Majority of conditions presenting wi stridor as a presenting symptom are due to caus at the level of larynx and above. Ten per cent of children presenting with stridor will have underlying cause below the level of larynx. neonates, the most common cause of stridor laryngomalacia followed by vocal cord paresi paralysis as the second most common cause. Select conditions which have airway obstruction ar intensive care implications will be described in t following section.

CONGENITAL MALFORMATIONS

Congenital malformations can affect the pediat airway in different ways. Many malformatio become evident in the delivery room others are n present until the child is older and somatic grow has made the airway impairment more evident.

Table 18.1: Causes of nasal obstruction

1. Posterior choanal atresia
2. Posterior choanal stenosis
3. Congenital nasal atresia
4. Midface hypoplasia (Apert's Syndrome, Crouzon's Syndrome)
5. Dermoid cyst
6. Nasal encephalocele
7. Nasal glioma
8. Nasal tumor
   i. Teratoma, hemangioma
   ii. Lipoma
   iii. Lymphoma
   iv. Neurofibroma
9. Naso-pharyngeal-fibroma
10. Rhabdomyosarcoma
11. Chordoma
12. Chondroma
13. Foreign body
14. Trauma
15. Scar tissue
16. Inflammation
17. Adenoid hypertrophy
18. NG tube with tape occluding other nostril.

Table 18.2: Causes of upper airway obstruction

Neonate and infant	*Older child*
Laryngomalacia	Laryngotracheobronchitis
Vocal cord paralysis	Supraglottitis (epiglottitis)
Malformation of laryngeal cartilages	Bacterial tracheitis
Subglottic hemangioma	Acute tonsillitis
Laryngeal web	Diphtheria
Vascular ring	Retropharyngeal abscess
Neonatal tetany	Peritonsillar abscess
	Glossitis Ludwig's Angina
Cervical spine abnormality	Subglottic edema
Macroglossia	Airway trauma
Down's syndrome	Airway burns
Beckwith Wiedemann syndrome	Laryngeal stenosis
Traumatic laryngeal edema	Adenoid hypertrophy
Choanal atresia	Mediastinal tumors
Craniofacial deformities	Airway tumors
Nasal encephalocele	Foreign body — Airway
Cystic hygroma	— Esophagus
Tracheo-esophageal fistula	Vascular ring
	Tracheobronchomalacia

Malformations of the Head

Macrocephaly

It is present in rhabdomyosarcoma, lymphangiomatosis of head and neck, in alteration of neural tube (encephalocele), in hydrocephalus, in metabolic diseases, in phacomatosis, in skull dysplasia and in megalencephaly.

Different malformations can be associated and can create specific syndromes.

- *Arnold-Chiari malformation* is characterized by hydrocephalus complicated by stretching of recurrent laryngeal nerve with consequent laryngeal obstructive syndrome.
- *Mucopolysaccharidoses* is associated with macroglossia, micrognathia, instability of atlas cervical vertebra, adeno-tonsillar hypertrophy, laryngeal and tracheal flaccidity, hypertrophy of submandibular tissues and hypomobility.

Facial malformations are rarely isolated and frequently appear as malformative syndromes.

Mandibular Hypoplasia

Mandibular hypoplasia is due to premature synostosis of cranial and facial sutures. It is present in acrocephalic syndactyly (Apert, Pfeiffer, Hallermann Streiff and Crouzon Syndromes). The head is characterized by prevalence of large and flat occiput, flat forehead and protruding bitemporal bones, skull alteration, depressed nose, hypertelorism and enophthalmos.

Malformations of central nervous system, of legs and arms, and cardiovascular system can be associated. Generally upper and lower airways are involved. Tracheomalacia, bronchomalacia, precocious consolidation of tracheal cartilage and tracheal stenosis appear.

Mandibular hypoplasia can be associated with atresia and choanal stenosis, reduction of the nose-pharynx space and malformations of palate (palatoschysis and bifid uvula).

Hypoplasia of jaw *(Pierre-Robin syndrome)* and other associated craniofacial abnormalities (e.g. *Treacher-Collins* and *Goldenhar* syndromes) are congenital defects that can lead to airway obstruction during spontaneous breathing and particularly during anesthesia. The anomalies tend to be less evident with age (4-6 years) but can create situations of difficult intubation and airway obstruction (Fig. 18.7).

Hyperplasia of jaw can hinder direct laryngoscopy. *Cherubism* is a familiar syndrome characterized by upper and lower jaw hypertrophy. Tongue dislocation makes visualization of glottis difficult during laryngoscopy.

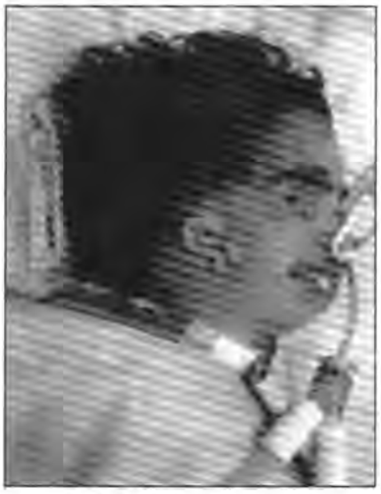


Fig. 18.7: Goldenhar syndrome

Dysfunction of Temporomandibular Joint

Congenital malformations are rare (agenesis of condyle) and generally follows trauma (forceps application during delivery) or inflammation (septic arthritis). Final result is reduced motility and anchylosis. Acquired micrognathia can be severe and can compromise jaw movements and mouth opening.

Airway management appears to be difficult in presence of micrognathia.

Malformation of Mouth and Tongue

1. *Microstomia,* reduced opening of the mouth, is present in several congenital malformations such as Freeman-Sheldom Syndrome, Hallermann Streiff Syndrome and Oto-palato-digital Syndrome. Acquired forms are connected with burns and caustic lesions. Microstomia hinders the introduction of laryngoscope blade, visualization of glottis and endotracheal tube positioning.
2. *Macroglossia* is present in congenital malformations such as *Beckwith-Wiedemann, Downs, Hurler and Pompe* Syndromes and in hypothyroidism, hemangioma and lymphangioma of the tongue. Lymphatic malformation generally involves submandibular space and neck but can be extended to tongue, vallecula, epiglottis and soft palate. If lymphangioma involves a large area of tongue, macroglossia can occur and the tongue may protrude from the mouth (Fig. 18.8).

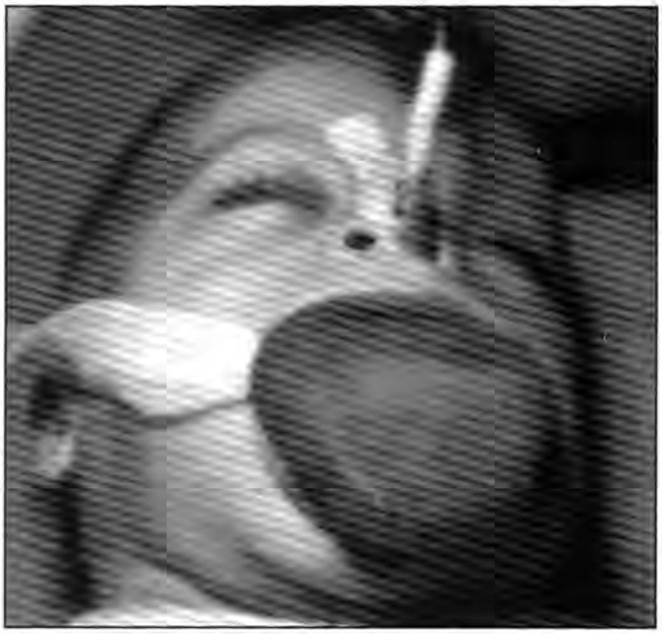


Fig. 18.8: Macroglossia

Macroglossia frequently creates airway obstruction and also dysphagia, dysphonia, orthodontic and aesthetic problems. Lymphangioma of the tongue can increase acutely after trauma and infection of upper airway. Patients may need tracheostomy for long time to maintain sufficient spontaneous breathing.

The base of the tongue can present extrinsic malformations such as tonsillar ectopia, ectopia of thyroid tissue and cysts of thyroglottic duct. Epiglottis can be dislodged over glottis creating obstructive syndrome.

Large tongue, reduction of oral cavity and reduction of submandibular space can result in airway obstruction and difficult laryngoscopy. Airway obstruction due to these pathological conditions can increase the incidence of sleep apnea.

Malformation of the Nose, Palate and Pharynx

1. *Choanal atresia,* unilateral or bilateral, results in respiratory distress shortly after birth because many infants breathe only through the nose and do not open the mouth when the nasal passages are occluded. Immaturity of coordination between respiratory efforts and oropharyngeal motor/sensory input accounts in part for obligatory nasal breathing. Clinical symptomatology is less evident in cases of unilateral presentation.

Obstructive symptomatology disappears during crying and reappears during feeding and in the absence of crying. These patients who survive the neonatal period come to the attention of doctors due to continuous nasal dripping or because during breathing the mouth remains open. Surgical operation is performed electively. Tracheal intubation is not mandatory and tracheostomy is usually not required.

It is frequently associated with other congenital malformations as palatoschisis, Treacher Collins syndrome or C.H.A.R.G.E. (Coloboma, Heart disease, Atresia of choane, CNS malformation, Genital Hypoplasia and Hearing anomalies or deafness) association.

2. *Nasal masses* are rare malformations and are consequent to embryonic malformations such as *encephalocele, glioma, dermoid cysts, cysts of nasolacrimal duct, tumor* and *inflammation.* These masses can create airway obstruction and direct laryngoscopy and intubation can be difficult. Intubation can be more difficult if it is associated to palatoschisis and the mass can invade the mouth. Nasal intubation is contraindicated, as is the use of nasal catheters.
3. *Palatoschisis* can be associated with difficult intubation. It is frequently associated with Pierre Robin, Treacher Collins, Goldenhar and Klippel-Feil syndromes. Special prosthesis which partially reconstruct the lip and palate can be useful for safe and easy intubation.

Malformation of Larynx

1. *Congenital atresia of larynx* is a life-threatening condition unless it is recognized immediately at birth and treated promptly. Indirect intubation of trachea can be performed in case of association with tracheo-esophageal cleft (Fig. 18.9).
2. *Laryngomalacia* is due to floppy soft laryngeal cartilages that lack rigidity. The glottis, the arytenoid cartilages and supraglottic structures prolapse toward the glottis during inspiration and this leads to partial obstruction and inspiratory stridor. Inspiratory stridor is exacerbated by crying or distress (Fig. 18.10). Over a 12 to 15 month period the cartilage gets rigid enough and the arytenoid prolapse may completely resolve.
3. *Laryngeal webs* occur at the level of glottis and usually are thin membranes that partially occlude the tracheal opening. It produces symptoms of feeble cry and dyspnea after birth (Fig. 18.11).
4. *Laryngeal cysts and laryngoceles* are soft tissues masses that protrude into the glottic lumen and result in inspiratory stridor (Figs 18.12 and 18.13).
5. *Vocal cord paralysis*, unilateral or bilateral, may be present at birth or acquired later. Left-sided cord paralysis is more common because of the lengthy path followed by left recurrent laryngeal nerve. Acquired vocal cord paralysis should derive from neurological disorders and postsurgery complications.

Vocal chord paralysis is the second most common cause of congenital obstruction of airways in children. Idiopathic forms, birth trauma of vagal

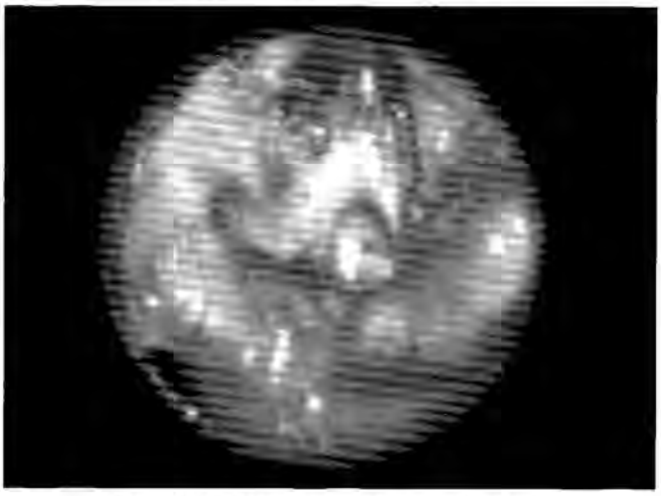


Fig. 18.9: Congenital atresia of larynx

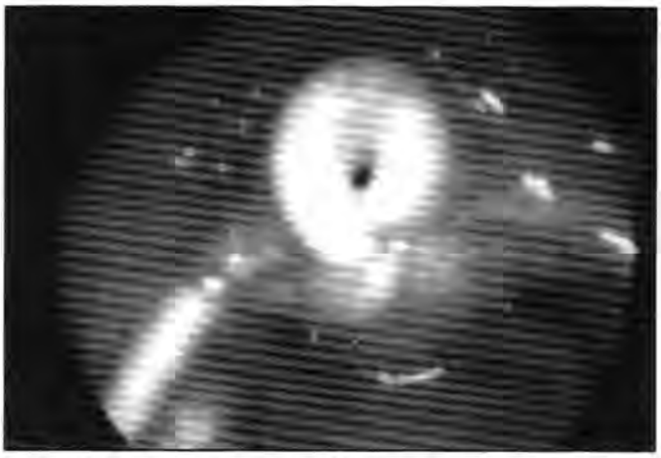


Fig. 18.10: Laryngomalacia: Complete obstruction during inspiration from supraglottis prolapse

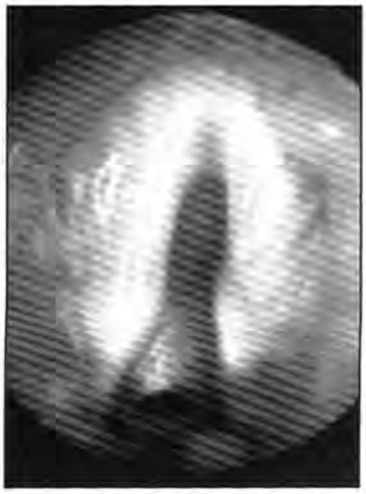


Fig. 18.11: Laryngeal web

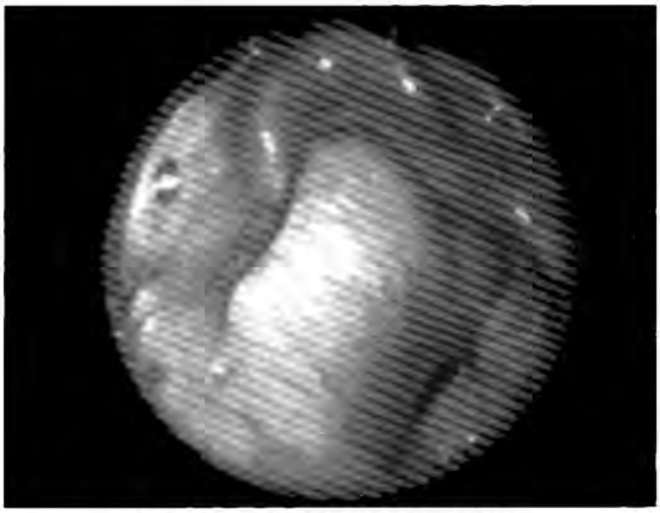


Fig. 18.12: Congenital laryngocele

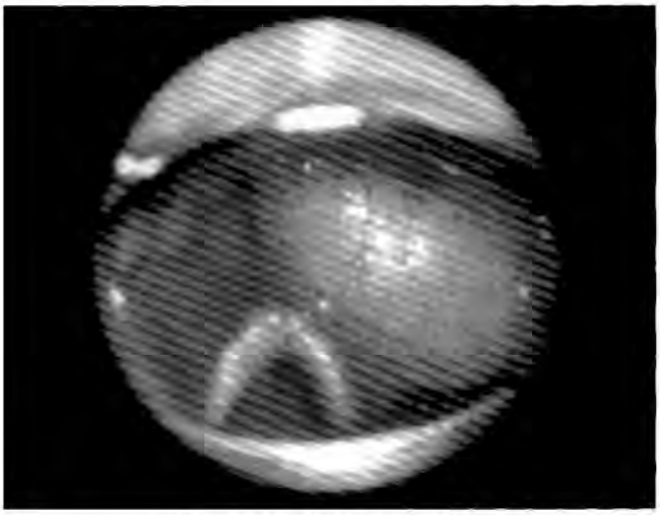


Fig. 18.13: Cyst of epiglottis

nerve, hydrocephalus, Arnold-Chiari malformation, encephalocele, thoracic and neck surgical operations are the most frequent causes.

Unilateral form can be asymptomatic while bilateral form can create inspiratory stridor, severe airway obstruction, cyanosis and apnea. Aspiration can be frequent in both unilateral and bilateral form.

Acquired forms generally resolve spontaneously, which is not the case for congenital forms. Unilateral form does not require treatment while bilateral car require intubation and/or tracheostomy.

Acquired Lesions of Larynx

Laryngeal granuloma is rare in pediatric age comparec to adults. It follows prolonged and traumati intubation but can also appear in patients intubatec for a short time. Symptomatology is progressive anc is characterized by hoarseness, stridor durin inspiration, voice alteration and dyspnea. Airwa obstruction is related to the size of the granulom which can obstruct laryngeal inlet and can creat respiratory distress. In cases of severe interary tenoidal adherence, the opening of glottis can b reduced, creating difficulty in positioning endc tracheal tube of suitable diameter for the specif patient (Fig. 18.14).

Congenital and Acquired Subglottic Stenosis

Congenital subglottic stenosis The infant may b asymptomatic at birth but often becomes symptomat when tracheal edema produced by a minor respir tory infection causes severe inspiratory stridor. Th

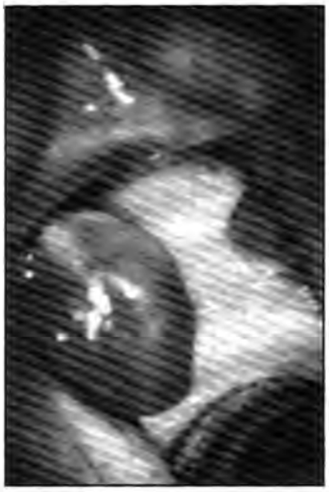


Fig. 18.14: Vocal cord granuloma

may be initially diagnosed as laryngotracheobronchitis (Fig. 18.17) but recurs with subsequent upper respiratory infection. This form can resolve spontaneously depending upon the severity of malformation.

Acquired subglottic stenosis Subglottic stenosis may be frequently acquired following tracheal intubation. Individual susceptibility, traumatic intubation, movement and size of endotracheal tube, use of cuffed tubes and duration of intubation can affect the severity.

Treatment of acquired subglottic stenosis is described at the end of the chapter. The most serious forms may require surgery or application of special stents and prosthesis.

Congenital laryngeal hemangioma involves subglottic area and can create severe airway obstruction. Stridor is frequent, as is alteration of voice tone, dyspnea, cyanosis and difficulty in feeding. Laryngoscopy shows the unilateral subglottic mass (Fig. 18.15).

Malformations of Trachea and Bronchi

Bronchomalacia and intrathoracic tracheomalacia The cartilaginous components of the upper airway lack their characteristic rigidity and the mechanism of breathing are altered due to an expiratory obstruction. Primary congenital tracheomalacia, which is rare, is caused by a congenital weakness or deficiency of the cartilage that supports the trachea and bronchi. Acquired tracheomalacia may occur from extrinsic compression of the airway and in long term ventilated infants. Suggestive symptoms are severe cyanotic episodes, often preceded by crying and agitation. Diagnosis can be made with airway fluoroscopy or bronchoscopy.

Laryngotracheoesophageal cleft is a congenital defect due to a failure of dorsal fusion of cricoid laminae, between the posterior laryngeal wall and, sometimes, the trachea and the esophagus. A severe form of the malformation is a persistent esophagotrachea, incompatible with the life (Fig. 18.16).

Tissue mass may reduce the caliber of tracheal lumen, either by extrinsic compression (e.g. *cystic hygroma*), or by growth into the tracheal lumen from the tracheal wall (e.g. *hemangioma*). The trachea may be compressed by the presence of an abnormal vascular structure. The innominate artery is the most common vessel causing tracheal compression. Vascular rings and slings, are other vascular abnormalities. Children present with various symptoms such as stridor, wheezing, and suffer from lobar atelectasis, or recurrent pulmonary infections. Congenital cysts and sequestration, bronchospastic disorders (e.g. asthma, bronchiolitis, bronchopulmonary dysplasia) can cause obstruction of airways.

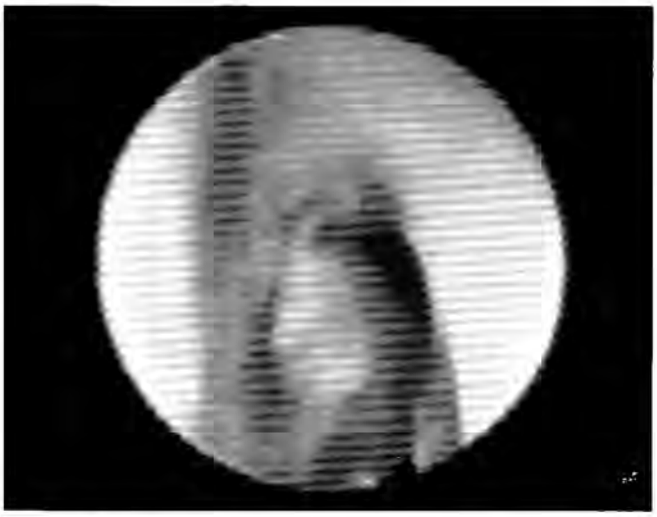


Fig. 18.15: Congenital laryngeal hemangioma

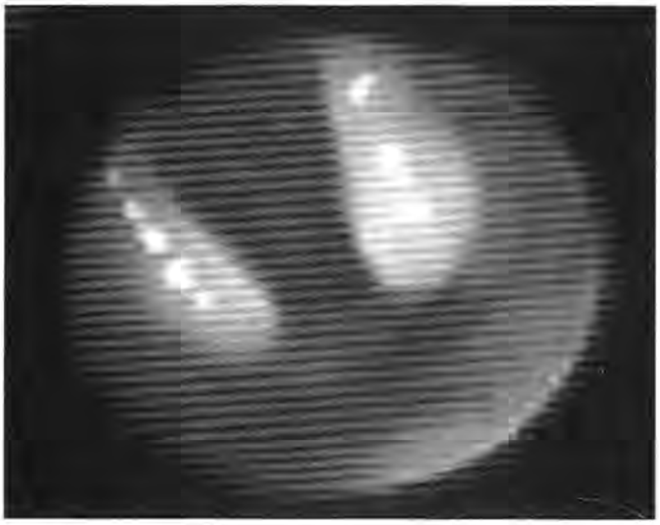


Fig. 18.16: Laryngotracheoesophageal cleft. Posterior wall of trachea is a genetic and communication exists through trachea and esophagus

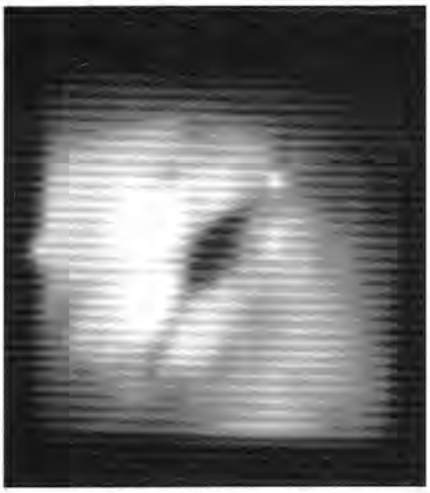


Fig. 18.17: Laryngo tracheobronchitis

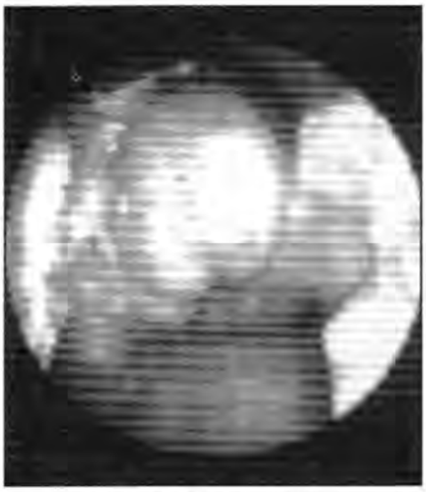


Fig. 18.18: Epiglottitis

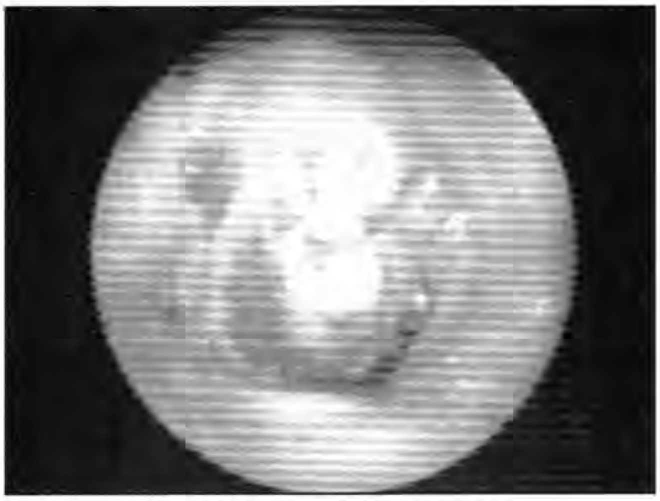


Fig. 18.19: Tonsillar hypertrophy

INFECTIOUS DISEASES

Diphtheria though rarely seen, remains importa in differential diagnosis of infectious causes airway obstruction due to inadequate immunizatio

Peritonsillar abscess is typical in the early secon decade of life and the child may present a muffle voice and drooling. If the abscess is sufficiently wid the child presents severe respiratory distress an trismus (Fig. 18.19).

Retropharyngeal abscess is characterized by progressive symptomatology with sore throat, fev and dysphagia. Posterior oropharyngeal wall ma bulge, but most commonly the findings a unremarkable. The rupture of the abscess can sp the contents into the tracheobronchial tree. A inspiratory radiograph of lateral neck may sho thickening of prevertebral soft tissue and possib mediastinal extension of infection.

Laryngeal papillomatosis is the most common benig tumor of the larynx between infancy and 4 years age and can cause severe respiratory obstructio which may be fatal.

SUPRAGLOTTITIS (EPIGLOTTITIS)

Supraglottitis (epiglottitis) is a life-threatening infe tion occurring predominantly in children betwee the ages of 9 months and 7 years, but may occasi nally affect adolescents and adults. It is now rarel seen since routine administration of hemophilu influenzae vaccine.

The acute inflammation involves the epiglott and aryepiglottic folds, producing a supraglotti The infection may start within the aryepiglottic fol and cause obstruction before involving the epiglotti The organism responsible is usually Hemophilu influenzae type B (Fig. 18.18).

Clinical Presentation

The child has high fever, drooling with a preferre position of sitting with head pushed forward to ha a less obstructed airway. Inspiratory stridor is n as striking as that seen in laryngotracheobronchiti it is softer and lower pitched. The voice and cry a muffled. Rapid and unpredictable progression of t disease may cause total acute airway obstruction.

is this feature of the disease that makes this condition one that requires urgent evaluation and treatment.

Differential Diagnosis

Supraglottitis should be differentiated from other significant life-threatening causes of upper airway obstruction. Usually the differentiation from laryngotracheobronchitis (croup) is fairly clear. However, it may be more difficult to differentiate from bacterial tracheitis (usually due to Staphylococcus aureus), in which inflammatory changes and thick inspissated mucopurulent secretions may cause life-threatening airway obstruction. Foreign-body aspiration should always be considered in any acute upper airway obstruction. The history, clinical examination, and X-ray findings provide clues to this diagnosis. A retro-pharyngeal abscess may present with acute upper airway obstruction. Occasionally, acute tonsillitis in severely hypertrophied tonsils may cause acute upper airway obstruction. Diphtheria, a rare but important bacterial infection occurring in the nonimmunized child, may be responsible for acute upper airway obstruction.

Management

A well-organized protocol is necessary for the management of the child with supraglottitis. Acute and total obstruction may be precipitated by crying and agitation in the child. The child should be allowed to assume the position of comfort and not be separated if being held by the parent in a comfortable position. Throat examination, arterial puncture for blood gas analysis, and placement of an intravenous line should be deferred until control of the airway has been secured by placement of an endotracheal tube or tracheostomy. The unpredictable progression of this disease and the significant risks of morbidity and mortality make placement of an artificial airway the safest course. The choice of artificial airway, that is endotracheal tube or tracheostomy, will depend upon the experience of the physician and the site where this procedure is performed. In most intensive care settings today, the choice is endotracheal intubation.

Radiography of the upper airway may be helpful in making the diagnosis of supraglottitis, and in differentiating it from laryngotracheitis or a radioopaque foreign body. However, if the child is in acute distress, X-ray procedures may delay life-saving intervention. An appropriate management plan consists of transferring the child from the emergency room to the operating room where, under controlled conditions, general anesthesia is administered for placement of the endotracheal tube with a surgeon (Pediatric surgeon or otolaryngologist) ready to perform an emergency tracheostomy should attempt at endotracheal intubation fail. In the procedure of tracheal intubation, prevention of hypoxemia and cardiovascular collapse is critical. Oxygen insufflation with laryngoscopy using a modified laryngoscope (oxyscope) may be helpful. Other centers perform endotracheal intubation in the pediatric intensive care unit (PICU). In skilled hands, the endotracheal tube may be placed nasotracheally with the aid of a flexible fiberoptic bronchoscope. Cultures of the blood and supraglottic structures are obtained once the artificial airway has been secured. Antibiotics (ampicillin and chloramphenicol or third-generation cephalosporins) are administered, and given for 10 days once organism sensitivity has been identified. On occasion, it may not be possible to establish an artificial airway either with an endotracheal tube or tracheostomy to ventilate the child. In this desperate situation, percutaneous cricothyroid membrane puncture and oxygen insulation may be lifesaving (Figs 18.20 and 18.21 A to J). Note however, that the cricothyroid membrane is extremely small in the

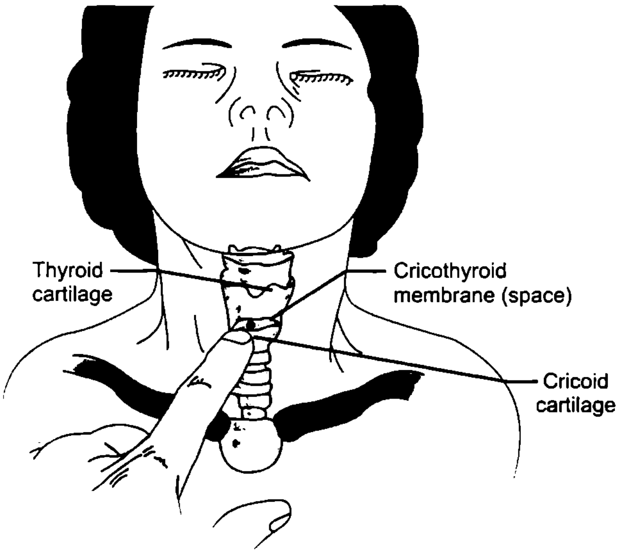
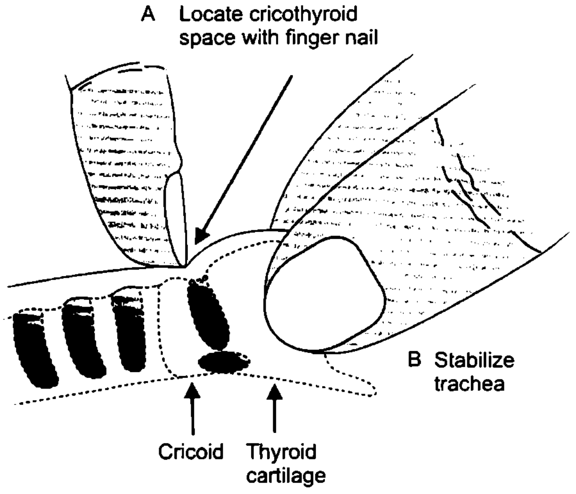
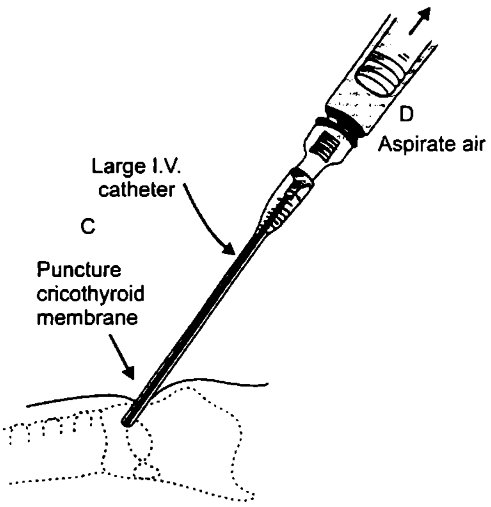


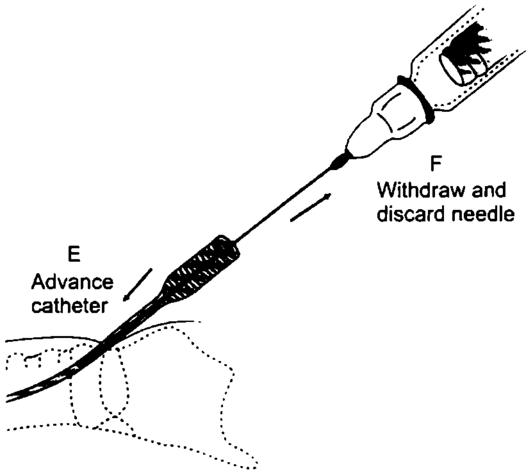
Fig. 18.20: Locate cricothyroid membrane just below thyroid cartilage and above cricoid ring


A Locate cricothyroid space with finger nail
B Stabilize trachea
Cricoid
Thyroid cartilage

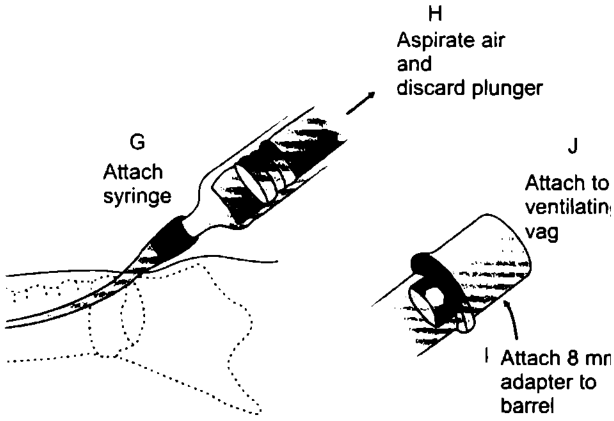
Figs 18.21A and B: Step for performing cricothyrotomy


D
Aspirate air
Large I.V. catheter
C
Puncture cricothyroid membrane

Figs 18.21C and D: Steps for performing cricothyrotomy


F
Withdraw and discard needle
E
Advance catheter

Figs 18.21E and F: Steps for performing cricothyrotomy


H
Aspirate air and discard plunger
G
Attach syringe
J
Attach to ventilatin vag
I Attach 8 mr adapter to barrel

Figs 18.21G to J: Steps for using cricothyrotomy for oxygen delivery and apneic oxygenation

infant and the procedure is more difficult t accomplish than in the adult. However, on rar occasions, one may have no choice! In most cases endotracheal intubation can be successfull performed and tracheostomy is rarely necessary After endotracheal intubation is performed, th patient is transferred to pediatric intensive care unit Extubation can usually be accomplished in 24-3 hours when the inflammation subsides causing a lea around the endotracheal tube. Direct laryngoscop may also be performed to visualize the epiglottis t make a decision to extubate.

Occasionally, pulmonary edema may be seen wit supraglottitis, as with other severe forms of acut upper airway obstruction. Metastatic complication of the H. influenzae infection are serious and mus be suspected when toxicity and fever do not resolv and when new symptoms appear. Metastati infections lead to pneumonia, meningitis, pericarditis, and periarticular abscess.

LARYNGOTRACHEOBRONCHITIS

Laryngotracheobronchitis (croup) is a very commo cause of acute upper airway obstruction in childre from 6 months to 5 years. The parainfluenza viru group appears to cause the majority of cases Influenza, Adenovirus and Respiratory Syncytia Virus have also been incriminated in some cases Inflammation and edema of the subglottic regio causes an increase in resistance to breathing. Th effect of narrowing the child's relatively small airwa causes a disproportionate increase in airway resis tance compared with the older child and adult. Laminar flow resistance at a given flow rate increases with the fourth power of the reduction in radius of the tube.

Clinical Presentation

The onset of laryngotracheobronchitis is insidious, with a history of upper respiratory infection characterized by a "barking cough" followed by inspiratory stridor. Low grade fever is common. The child is tachypneic with chest retractions. With progression of the disease, the child may get cyanosis. This indicates severe hypoxemia due to ventilation-perfusion mismatching. Increasing tachypnea, tachycardia, increasingly more severe sternal and chest retractions, and deepening cyanosis may occur and signal life-threatening airway obstruction. Croup score has been used to objectively assess the severity of upper airway obstruction based on presence of inspiratory stridor, severity of retractions, air entry, cyanosis and level of consciousness." The score may be affected by interobserver variability. Roentgenograms of the upper airway (particularly the anteroposterior view) showing subglottic narrowing may be helpful when the history and examination are atypical.

The differential diagnosis must consider other causes of a severe acute upper airway obstruction, namely, supraglottitis, bacterial tracheitis, a foreign body, subglottic hemangioma, or diphtheria.

Management

In the majority of cases, management includes allaying patient and family anxiety, and providing oxygen therapy to treat hypoxemia. Humidified air therapy is widely used but lacks support in scientific literature." Antibiotics have no role in treatment of croup. Inhalation of racemic epinephrine (0.5 ml in 3 ml saline) may benefit the child on a short term basis. This form of treatment probably does not affect the duration or ultimate severity of the child's illness. The treatments may need to be repeated every 1 to 3 hours. Rebound airway swelling may result 45 minutes to 1 hour after racemic epinephrine treatment; therefore, close observation of the patient for airway obstruction and cardiovascular symptoms is necessary. Epinephrine nebulization may be used if racemic epinephrine is not available in the same dosage as that of racemic epinephrine. Dexamethasone in dosage of 0.5 mg/kg intravenously may be used 8 hourly. Nebulized steroid preparations such as budenoside or fluticasone may also be used.

Increasing distress in the child manifested by progressive tachycardia, tachypnea, stridor and cyanosis warrant more active measures to relieve potential life-threatening airway obstruction. With increasing airway obstruction and fatigue, the child may not generate vigorous respiratory efforts and therefore stridor may diminish. This may erroneously be interpreted as improvement in the child's condition. Depression of the level of consciousness and decreased muscle tone are important clinical signs of critical deterioration. Decision to perform endotracheal intubation is therefore based on clinical assessment revealing worsening airway obstruction. Skilled personnel are essential when performing this maneuver. In some situations, progressive respiratory distress is compounded by the presence of thick inspissated secretions that the child is unable to cough up. Tracheal intubation provides a means for suctioning the airway and maintaining patency. The endotracheal tube should be a 0.5 mm to 1.0 mm internal diameter smaller than would normally be used in order to avoid ischemic necrosis in the subglottic area with potential subsequent stenosis. Nasotracheal intubation has been extensively used. Based on our experience, when required, endotracheal intubation can be used as successfully as nasotracheal intubation and tracheostomy is rarely necessary. Extubation is carried out in the pediatric ICU after 3 to 5 days or earlier if an air leak develops around the endotracheal tube at approximately 20 cm of water pressure. The use of helium-oxygen (Heliox) mixtures in the management of acute upper airway obstruction due to croup was practiced many years ago. There has been a recent renewal of interest in this method of treatment. While endotracheal intubation or tracheostomy remains the definitive treatment for life-threatening airway obstruction, this technique may be helpful in guiding the child through a crisis so that definitive therapy may be carried out under more optimally controlled conditions. A limitation of this technique to be kept in mind is that the fractional concentration of oxygen in "Heliox" is only 30-40 percent therefore limiting its use in severely hypoxemic conditions requiring higher FiO_2.

BACTERIAL TRACHEITIS

Bacterial tracheitis is also referred to as pseudomembranous croup and membranous croup. It is considered a primary infection most commonly due to staphylococcus aureus. Occasionally H Influenzae, streptococcus and Branhamella catarrhalis have been identified. Severe subglottic edema with tracheal mucosal sloughing occurs. This is associated with copious mucopurulent secretions and inadequate mucociliary clearance, and may rapidly lead to serious and potentially life-threatening airway obstruction.

Clinical Presentation

The disease affects infants and children until early adolescence. It usually starts with an upper respiratory infection which rapidly progresses over hours with the child becoming acutely toxic and severely distressed. High fever, hoarseness, stridor and cough are prominent and airway obstruction may lead to hypoxemia and death. The child may have pulmonary infiltrates on chest roentgenogram and becomes rapidly exhausted and unable to clear the airway. Establishment of an artificial airway by tracheal intubation is usually necessary. Bronchoscopy may be helpful in clarifying the diagnosis and clearing the airway of sloughing debris. Intensive airway care is essential to prevent obstruction of the child's own airway as well as the endotracheal tube. A combination of IV nafcillin (or cloxacillin) and a third generation cephalosporin is usually adequate. Bacterial tracheitis should be considered in the differential diagnosis if the child does not respond to conventional therapy for croup.

FOREIGN BODIES

Foreign body aspiration may cause acute life-threatening airway obstruction or if initially undetected result in severe lung damage.'—"Children in the first two to three years of life are particularly prone to aspirate a wide array of foreign objects. Eighty per cent of cases occur under 4 years of age and aspiration occurs twice as commonly in males. Sixty-five per cent of food asphyxial deaths occurre in infants younger than 2 years of age."

Peanuts, gram, and popcorn are among the mo common offenders. Most lodge in a main or ste bronchus; right more often than the left (Fig. 18.22 Sharp foreign bodies include plastic, and pins. The can impact in the larynx and produce symptoms acute laryngeal edema. One should also suspect th "a foreign body aspiration" may be multiple foreig bodies. Foreign bodies are also subject to movemen from their original position. Foreign body aspiratio of a balloon has been reported in a 3-month ol infant. Therefore, foreign body aspiration must b considered in all cases of sudden respiratory distres regardless of age.

Clinical Presentation

In two thirds of children, the diagnosis is mad within the first few days. In a significant numbe however, there are no symptoms. Thus, the clinic picture is modified by the interval that has elapse from the time of foreign body aspiration. There ma be a history of violent coughing, gagging and seve respiratory distress with cyanosis. Wheezing ma be present. However, the diagnostic triad wheezing, coughing and decreased breath sound over the affected side are more commonly encou tered in the late diagnosed case. The diagnostic tria is incomplete in 61 percent of aspirating patient

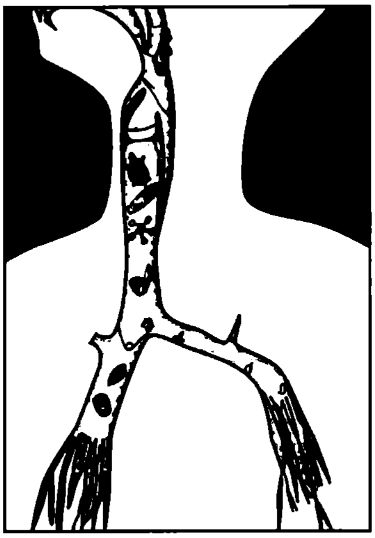


Fig. 18.22: Various foreign bodies in the airway
(For color version see Plate 6)

Cough and wheezing may persist without respiratory distress. These patients may be frequently diagnosed as having chronic asthma.

Chest roentgenograms and fluoroscopy are important diagnostic procedures. It should be appreciated that the majority of aspirated foreign bodies are not radio-opaque. Atelectasis or obstructive emphysema may be seen on the obstructed side (Fig. 18.23). Hyperinflation may be enhanced by forced expiration. In some situations, the movement of the foreign body and its breaking up into fragments may produce atelectasis followed by hyperinflation. Recurrent persistent localized pneumonitis that does not respond to standard medical therapy requires investigation for an underlying foreign body. More than half of the patients with aspirated foreign bodies are diagnosed late when there is evidence of significant airway obstruction and an associated history of choking. *CT chest* followed by a *bronchoscopy* may be necessary when diagnosis is not clear.

Foreign bodies impacting in the esophagus especially at sites of anatomical constriction namely, the post-cricoid region and at the level of the aortic arch, may produce compression of the trachea and serious airway obstruction.

Management

The pediatrician should be familiar with emergency measures to dislodge a foreign body which is producing a life-threatening crisis. Debate continues over the various maneuvers. The Academy of Pediatrics (Section of Accident and Poison Prevention) recommends back blows followed by abdominal thrusts. Back blows have been blamed by some investigators for causing further distal impaction for the foreign body. Abdominal thrusts (Heimlich maneuver) have been known to be effective. In infants, liver trauma is possible with abdominal thrusts and hence chest thrusts are recommended. Blind finger sweeps to remove foreign body from pharynx are not recommended. The Storz pediatric bronchoscope with the Hopkins rod lens telescope provides excellent visualization of the foreign body and allows introduction of a forceps to remove the foreign body. On occasion, a Fogarty embolectomy balloon catheter has been used to dislodge an impacted foreign body. The catheter is pulled back together with the bronchoscope to the pharynx from where the foreign body is removed. Rarely the foreign body, if deeply lodged in the bronchus, may have to be removed via a thoracotomy and bronchotomy. Extraction may be difficult with foreign bodies that tend to crumble, e.g. peanuts. Following removal of the foreign body, the child may still have symptoms due to the presence of residual foreign bodies. Flexible fiberoptic bronchoscopy appears to be a useful technique in this situation to screen for residual foreign body fragments. More recently fiberoptic bronchoscope with basket removal of foreign bodies has been used successfully. A rigid bronchoscope should be available whenever a foreign body removal is attempted. *Current recommendation to remove foreign bodies from pediatric airways includes the use of rigid bronchoscope in combination with flexible bronchoscope (to visualize distal fragments).* Following a difficult removal of a foreign body, the child may have residual glottic and airway edema and require steroid therapy and racemic epinephrine inhalations. The use of steroids, while frequently advocated, remains uncertain. A pneumomedistinum or pneumothorax may occur due to airway injury caused by the foreign body per se or during its removal.

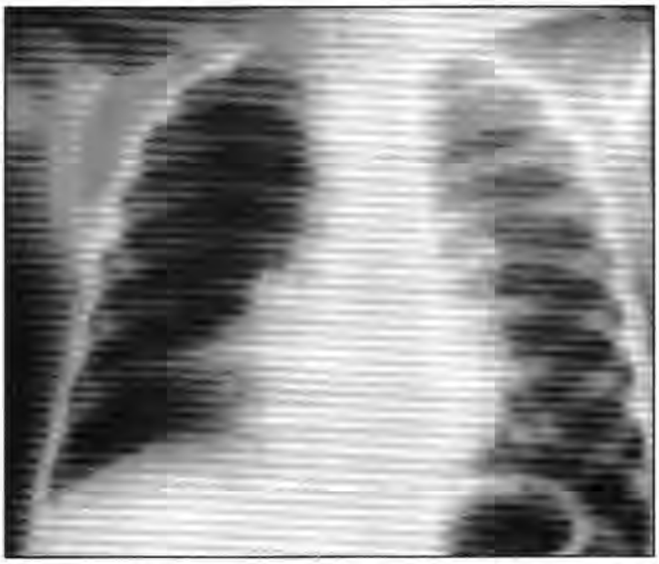


Fig. 18.23: Chronic right middle lobe infitrate indicative of foreign body

TRAUMATIC INJURY

Traumatic injury to the upper airway may be divided into orofacial trauma and laryngeal or tracheal trauma. Orofacial trauma increases the risk of upper airway obstruction. The swelling of soft tissues and inhalation of blood may lead to airway compromise. Injury to the larynx and trachea may occur following blunt trauma such as road accident or following penetrating trauma. The development of subcutaneous emphysema is evidence that a laryngeal fracture or tracheal tear has occurred.

BURN INJURY

Burn injury of upper airway may complicate the management of a burn victim.[3] Because of the very efficient cooling capacity of the upper air passages, thermal injury to the airway below the vocal cords is uncommon occurring in less than 5 per cent. This injury should be strongly suspected in all patients with facial burns and airway should be secured early because of risk of worsening airway edema and facial swelling leading to upper airway obstruction and difficulty in intubation at a later stage. Airway compromise can occur during administration of sedation and analgesia for the purpose of frequent major burns dressings.

ANGIOEDEMA

Angioedema is a well-localized edema involving the deep layers of skin, including the subcutaneous tissue. It may occur in response to a variety of systemic disorders and may lead to swelling of the soft tissue of the face, particularly the eyes and lips. If the edema involves the soft tissues of the upper respiratory tract, laryngeal obstruction may result.

Airway obstruction can also be associated with various facial and neck malformations in which airway patency can be lost from infective origin or reduction of the muscle tone of the neck.

TRACHEAL STENOSIS

Tracheal stenosis in infants and children may be congenital or acquired.

Congenital Tracheal Stenosis

Congenital tracheal stenosis is a rare life-threatening condition. Pathologically, the luminal narrowing is due to the presence of complete tracheal rings as opposed to C-shaped cartilaginous rings. In 5
percent of cases, congenital tracheal stenosis i
associated with pulmonary artery sling wher
compression and narrowing of the posterior trache
wall is due to the anomalous origin of the le
pulmonary artery from the right pulmonary arter
The anomalous left pulmonary artery passes behin
the trachea to supply the left lung. Surgical correctio
of the vascular anomaly leaves the child with trache
stenosis because of the underlying tracheal defec
In other vascular anomalies, compression of th
trachea may also occur, e.g. double aortic arch. Her
correction of the vascular anomaly will largel
improve the airway problem. However, this i
variable and some infants continue to hav
respiratory difficulty for prolonged periods. In som
cases, the ligamentum arteriosum is responsible fc
the compression and remains unsuspected becaus
it will not be visualized on an angiogram. Innominat
artery compression of the trachea may be sever
enough in some children to cause significar
narrowing of the airway lumen. Aortopexy in th
situation relieves the airway occlusion.

Acquired Tracheal Stenosis

Acquired tracheal stenosis occurs in a number c
different circumstances": (1) postintubation (endotr
cheal tube or tracheostomy), (2) post-trauma, (
thermal and chemical burns, (4) primary tumo
(rare).

Tracheal stenosis is relatively uncommon in ne
nates, being more frequently encountered in old
children. Tracheal pressure necrosis from th
endotracheal or tracheostomy tube leads to mucos
injury, the formation of granulation tissue, pericho
dritis and finally, scar formation with strictur
Symptoms of obstruction are delayed following t
removal of the tube.

Clinical Presentation

Congenital tracheal stenosis must be considered i
any infant who has episodes of stridor, cyanosi
wheezing, recurrent pneumonias or sudde
respiratory arrest. Symptoms may appear at bir
or shortly thereafter as the stenosed airway becom
inadequate for the growing child's greater venti
tory needs. Following upper respiratory infectio

mucus plugs and inflammatory reaction may acutely precipitate respiratory failure. Respiratory distress, stridor, and retractions increase with agitation and crying in the child as a result of dynamic collapse of the airway associated with increased respiratory efforts. Airway obstruction is aggravated by the inability to clear mucus. Depending on the site of tracheal obstruction, wheezing may be heard and may be misdiagnosed as "allergic asthma". Thus a thorough history is necessary and a suspicion of this complication should exist if there is a history of recent tracheal intubation or tracheostomy and, particularly, if a diagnosis of asthma has been made which has not responded to standard therapeutic maneuvers. Examination of the child should include a search for other anatomic anomalies, especially vascular. This includes *barium swallow, echocardiography and in selected cases, angiography.*

Roentgenograms of the anterior-posterior and lateral cervical and chest views provide visualization of the location and extent of the tracheal pathology. *Airway fluoroscopy* demonstrates the dynamic movements of the airway with respiration and any associated degree of tracheomalacia. Tracheobronchography is potentially dangerous because of possible reaction to the contrast material causing further obstruction of the airway. *Computerized tomographic scans* can delineate tracheal dimensions, the extent of the stenosis and also mediastinal and vascular pathology. Patients undergoing these studies who have an endotracheal tube in place may be at grave risk if extubated for the radiologic study. A physician skilled in airway control should be in attendance at the X-ray facility to replace the endotracheal tube if necessary.

Management

Bronchoscopy is performed for the definitive diagnosis and the trachea may then be dilated. Airway bleeding and edema may occur leading to increasing respiratory difficulty after the dilatation. This should be anticipated. The child should be observed in the intensive care unit following the procedure. Inhalation of racemic epinephrine may alleviate some obstruction due to edema. However, progressively increasing distress from obstruction may necessitate tracheal intubation. Prior to intubation if this is required, positive pressure with a face mask, 100 percent oxygen and an adjustable "pop-off" PEEP valve can force oxygen into the lungs by counteracting the dynamic airway collapse which occurs with increasing respiratory efforts.

The child should remain in an intensive care unit, where airway compromise may be carefully monitored and treated should deterioration occur. With significant airway obstruction, narcotics and sedatives should *not* be given as they may cause central respiratory depression and precipitate acute respiratory failure. In selected cases clinical, radiologic and endoscopic evaluation may be all that is required in assessing the need for conservative management or surgical correction. If the child is relatively stable then conservative management is preferred delaying surgical resection until the child is at an age when tracheal resection would be considered a safer procedure.

A variety of techniques have been utilized before undertaking tracheal resection in selected cases. These include *dilatations, steroid injections, resecting with diathermy, cryosurgery, and laser therapy.* These techniques may be helpful while granulation tissue is present or while the scar is still in the early stages. Once the scar tissue becomes hard and fibrous then resection would appear to offer the best chances for success. Resection of tracheal stenosis is possible even in small infants.

As much as 50 percent of the trachea may be resected and a primary anastomosis performed. However, with extensive tracheal stenosis newer techniques such as the use of cartilage grafts, pericardial patch, and stents made of a flexible steel spring coated with silicone rubber, have been employed.

It is usually possible to extubate the child at the conclusion of surgery. This is preferred as the presence of the tube (a foreign body) in the trachea may predispose to breakdown of the anastomosis. However, should the child have to remain intubated, endotracheal tube positioning is critical as the infant's shortened trachea and flexed head may predispose to accidental main stem bronchial intubation or extubation with minimal movement.

TRACHEOMALACIA

Tracheomalacia is a condition of abnormal flaccidity of the tracheal wall leading to tracheal collapse during respiration. Congenital tracheomalacia as a primary defect is uncommon. The use of flexible ribreoptic bronchoscopy has allowed the visualization of the airway dynamics in the child with respiratory distress and has revealed a more frequent occurrence of tracheomalacia than previously suspected. In this situation, there is a congenital malfonnation of the tracheobronchial cartilages such that they provide Inadequate support and allow expiratory collapse. The condition may be associated with tracheoesophageal fistula where there is deficiency of tracheal cartilage or when extrinsic compression occurs with vascular anomalies and mediastinal masses. It may occur with systemic diseases affecting cartilage and connective tissue; namely, Ehlers-Danlos syndrome. Acquired tracheomalacia follows tracheostomy and prolonged tracheal intubation, especially with cuffed endotracheal tubes.

Clinical Presentation

In primary tracheomalacia, the symptoms of respiratory distress manifested by stridor and cyanosis appear after the first few weeks of life, aggravated by infections and agitation. Spontaneous resolution takes at least 2 years. The clinical history of previous intubation or tracheostomy may suggest this diagnosis in a child who has symptoms of airway obstruction that is aggravated by stress, crying and agitation. Airway fluoroscopy defines the dynamic aspects of tracheomalacia, that is constriction and dilatation of the tracheal wall related to phases of respiration. Bronchoscopy at *light* levels of anesthesia confirms the radiologic findings. Fiberoptic bronchoscopy using sedation and local anesthesia provides the best indication of the child's airway dynamics under "normal" conditions. The natural tendency for the trachea is to stiffen with time, usually by two years of age, and thus surgery is rarely indicated. However, underlying causes for secondary tracheomalacia should be identified and treated. Occasionally, tracheostomy may be required until the trachea has firmed and stabilized. Those children requiring tracheostomy to maintain a safe, clear airway appear to take longer to stabilize their airways. In selected cases, vascular suspension of the aorta or innominate artery relieves the problem. Long term (approximately 24 months) positive-end expiratory pressure (PEEP) of 8-10 cms H_2O (via a non-invasive ventilator) or via a tracheostomy tube has been effective in stabilizing the upper airway until the tracheal wall has become firm and less compliant. Tracheomalacia may extend into the main stem bronchi (bronchomalacia). Surgical treatment using an implanted synthetic graft has been successfully carried out apparently without compromising airway growth. Bronchial stents are also available if the tracheomalacia is co existing with bronchomalacia.

MEDIASTINAL MASSES

Mediastinal masses occur in the anterior, middle and posterior mediastinum. Common mediastinal masses according to location are:

a. *Anterior mediastinum*: lymphoma, teratoma, cystic hygroma, pericardial cyst, diaphragmatic hernia (via foramen of Morgagni)
b. *Middle mediastinum*: lymphoma, tuberculous lymphadenopathy
c. *Posterior mediastinum*: neurogenic tumor (neuroblastoma, ganglioneuroma, neurofibroma) esophageal duplication, bronchogenic cyst, diaphragmatic hernia (via foramen of Bochdalek).

Of concern is the effect of mediastinal masses on the airways, lungs and cardiovascular system. Anesthesia, bronchoscopy and surgery in these patients is potentially hazardous and therefore thorough investigation and preparation is mandatory.

Anterior Mediastinum

Anterior mediastinal masses may produce severe respiratory and cardiovascular complications. Obstruction of major airways, cardiac compression producing tamponade and superior vena caval obstruction may occur. Malignant lymphoma may surround the heart with infiltration of the pericardium, producing pericardial tamponade: Most anterior mediastinal masses are lymphoid in origin (Hodgkins and nonHodgkins lymphoma). It is important to appreciate that cervical masses, e.g., cystic hygroma may extend into the mediastinum.

Posterior Mediastinum

Posterior mediastinal masses, e.g., esophageal duplication cyst, may cause respiratory distress through pressure on adjacent lung. In addition, compression of the esophagus can lead to dysphagia and possibly reflux and aspiration.

Symptoms may be incorrectly attributed to benign and chronic conditions. For example, a child with "asthma" unresponsive to treatment with bronchodilators was shown to have a large mediastinal mass (neurogenic tumor) obstructing the airway.

Anesthetic and Intensive Care Implications

Preoperative preparation of the child with a mediastinal mass includes evaluation of the degree of airway obstruction and any possible cardiovascular compromise. In addition to clinical evaluation of airway patency and hemodynamic stability, other special studies are carried out. Roentgenograms of the airway might include tomography and fluoroscopy. Computerized tomography (CT) scans of the airway provide better definition of obstruction. Pulmonary flow-volume loop studies, both in the upright and supine position are sensitive indicators of obstructive lesions of the major airways. Peak now rate may show a significant decrease even when the CT scan has revealed no airway obstruction.

In evaluating hemodynamic stability, the possibility of cardiac tamponade must be considered;" thus, it is important to examine for pulsus paradoxus. Echocardiography and barium swallow examinations are performed in selected cases.

In some cases, especially in Hodgkins disease, where compression of the trachea and bronchi by the mediastinal mass is perceived as life-threatening, irradiation of the tumor prior to anesthesia may ameliorate the degree of airway obstruction and provide a safer induction. General anesthesia and especially the use of muscle relaxants in these patients may be extremely hazardous. In the absence of spontaneous respiration, they may be extremely difficult to ventilate even with an endotracheal tube in place. Local anesthesia in preference to general anesthesia should be used for the biopsy procedure if suitable. In rare situations, standby cardiopulmonary bypass is necessary. Thoracotomy is usually necessary to make the specific diagnosis. Excision of the entire mediastinal mass is undertaken if possible. Irradiation of the tumor distorts the cellular picture and interferes with making a clear histologic diagnosis. Hence, a practice of general anesthesia prior to irradiation of anterior mediastinal masses has been proposed even in the presence of respiratory or cardiovascular symptoms.

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CHAPTER

19

Meconium Aspiration Syndrome and PPHN

Manish Malik, Praveen Khilnani

INTRODUCTION

Meconium is derived from the greek word 'mekoni', meaning poppy juice or opium. Aristotle first described the association between presence of meconium stained amniotic fluid and a sleepy fetal state in utero.[1] Meconium aspiration syndrome (MAS) results from the inhalation of meconium in-utero, at the time of birth or soon after delivery.[2,3]

The passage of meconium in-utero resulting in meconium staining of liquor occurs in 10-15 percent of all deliveries. The inhalation of meconium into the tracheo-bronchial tree resulting in MAS occurs in 5 percent of these infants. Incidence between 1-5: 1000 has been reported. A recent study showed 0.43 per 1000 babies needed intubation and ventilation with a primary diagnosis of MAS. Of these 34 percent were more than 40 weeks gestation and 51 percent had documented fetal distress needing obstetric intervention. 42 percent of these babies were born by cesarean section.[4,5] Improved perinatal management has led to a decline in the incidence of MAS in the developed world.

Pathophysiology of MAS (Fig. 19.1)

MAS is primarily a disease of term and post-term babies. Fetal hypoxia and fetal maturity beyond term are the two main associations leading to MAS. Meconium staining of amniotic fluid is rarely seen in preterm delivery. An incidence of 5 percent is reported along with an association with chorioamnionitis. A recent 7 year study showed an incidence of 4 percent in preterm delivery with increased risk of periventricular hemorrhage in these babies.[6] However there was no association with listeriosis as traditionally believed.

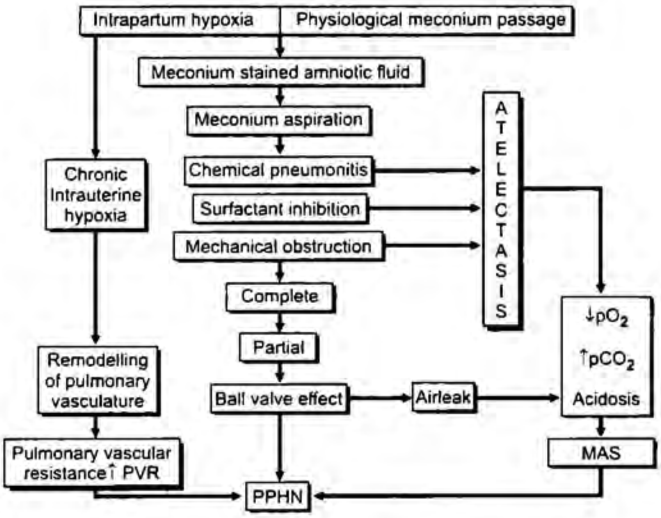
Intrapartum hypoxia
Physiological meconium passage
Meconium stained amniotic fluid
Meconium aspiration
Chronic Intrauterine hypoxia
Chemical pneumonitis
Surfactant inhibition
Mechanical obstruction
Complete
Partial
ATELECTASIS
↓pO₂
↑pCO₂
Acidosis
Remodelling of pulmonary vasculature
Ball valve effect
Airleak
Pulmonary vascular resistance↑ PVR
MAS
PPHN

Fig. 19.1: Pathophysiology of meconium aspiration syndrome (MAS) and persistent pulmonary hypertension of newborn (PPHN)

Fetal stress stimulates intestinal peristalsis and relaxation of the anal sphincter leading to the passage of meconium. With increasing maturity there is an increase in the production of prokinetic hormones, mainly motilin resulting in passage of meconium in post term babies.

Prolonged fetal hypoxia stimulates fetal gasping resulting in the aspiration of meconium prior to delivery. After delivery inhalation occurs if the oropharynx and larynx are full of meconium at the time of the first few breaths.

Meconium is thick and viscous causing damage to the lungs due its physical and chemical properties. It is primarily composed of water mixed with intestinal secretions, cell debris, lanugo hair, bile salts and bile pigments. Meconium also contains pancreatic enzymes including phosholipase A2 which is a potent inducer of inflammatory injury to the lung.

Particulate meconium can completely obstruct the proximal airways resulting in atelectasis. This causes ventilation-perfusion mismatch and can lead to severe acute hypoxia. Partial obstruction of distal airways results in a ball valve effect allowing air into the airways but preventing its exhalation. This air trapping leads to overdistension which is further complicated by pneumothorax, pneumomediastinum and interstitial emphysema.

Chronic in utero hypoxia results in abnormal muscularisation of pulmonary vasculature. Hypoxia and acidosis further contribute to vasoconstriction leading to increased pulmonary vascular resistance. This results in extrapulmonary shunting of blood leading to features of persistant pulmonary hypertension of newborn (PPHN).[7,8]

Meconium aspiration is now largely believed to be an intra partum event. Any meconium in the oro-pharynx should be cleared after delivery of the baby's head and prior to the delivery of the shoulders. This prevents aspiration of meconium when the baby takes its first few breaths. This traditional teaching has recently been challenged by a multi-centric randomized controlled trial which showed no benefit of oropharyngeal or naso-pharyngeal suctioning performed prior to delivery of shoulders in terms of respiratory outcome. 2005 Neonatal recommendations of American heart association (AHA) and the American Academy of Pediatrics do not recommend suctioning of the mouth, nose and pharynx before the delivery of the shoulders in meconium staining.[9-12]

Intubation and suctioning of meconium from the trachea is no longer recommended in vigorous babies. These recommendations are based on a Cochrane review of 4 randomized controlled trials showing no benefit of this procedure . If the infant is not vigorous, has absent or depressed respiration, has reduced muscle tone or has a heart rate of less than 100/minute intubation and suctioning of trachea should be performed before other resuscitative steps.[12]

Clinical Manifestations

Babies with MAS present with respiratory distress Respiratory rates may be as high as 100-120/minute Increased work of breathing is manifest by use of accessory muscles of respiration along with subcostal and intercostal recession. Babies may have varying amounts of oxygen requirements. At the most severe end of the spectrum is hypoxic respiratory failure needing ventilation. The chest appears hyperinflated with increased antero-posterior diameter. Chest X-ray usually shows patchy infiltrates with varying degree of atelectasis. Air leaks are a common finding in MAS. Clinically expiratory grunt may be manifest with widespread crepitations and occasional rhonchi on auscultation.

Associated myocardial damage secondary to asphyxia can lead to hypotension. PPHN is a common complication in severe MAS and is often the cause of mortality in such cases. Management of PPHN involves minimal handling, adequate sedation with correction of hypoxia and acidosis. Blood pressure must be maintained. Dobutamine is preferred over dopamine if echocardiography suggests a low left ventricular output. Persistent hypoxia out of proportion to the expected degree of parenchymal lung disease should be investigated for possible PPHN . Clinically, this can present as intermittent cyanotic spells as systemic PaO_2 alters with the amount of shunting. Clinical examination of the heart may reveal a single loud S2 (normal "splitting" resumes when pulmonary hypertension subsides) These clinical features may be the only diagnostic tool available in developing countries. Hyperoxia test, preductal and post ductal PaO_2 analysis and hyperoxia hyperventilation test may be useful Echocardiography when available is confirmatory

If PPHN develops S2 may be single and a murmur of tricuspid regurgitation may be present. PPHN should be suspected if there is severe intractable hypoxia with pre and post ductal oxygen saturation difference of > 10 percent or pre and postductal pO_2 difference of >20 mmHg. Echocardiography provides confirmatory evidence in the form of elevated pulmonary artery pressures on doppler with extrapulmonary right to left shunting of blood.

Renal function may be impaired secondary to hypoxic damage. Coagulopathy may result as a result of liver dysfunction. Neurological status must be closely observed because of associated hypoxic encephalopathy and seizures.

Management Strategies

General

A policy of minimal handling of sick babies must be adopted as handling and agitation can worsen gas exchange. Hypoxia also induces pulmonary vasoconstriction hence higher saturations are desirable. Adequate analgesia and sedation must be used to keep the baby comfortable if ventilated. With the widespread use of synchronized modes of ventilation, paralysis is reserved for the baby who is fighting the ventilator despite adequate sedation.

Ventilatory Options

A strategy of long expiratory time with low PEEP is used to minimise air trapping and overexpansion of the lungs. Gentle ventilation with relatively higher pCO2 of 50-55 mmHg may be acceptable, provided pH is >7.2. Aim to keep pH > 7.25-7.30 to reduce pulmonary vascular resistance.

High frequency oscillatory ventilation (HFOV) can be tried if conventional ventilation is failing. It helps in recruitment of alveoli and improves CO_2 elimination. HFOV improves oxygenation and outcome specially when used with inhaled Nitric Oxide.[13-17]

All strategies using various combination of hyperventilation with lower tidal volumes, open the lung and keeping the lung open strategies with conventional ventilation, use of pulmonary vasodilators such as tolazoline,[18] sildenafil, nitric oxide, use of high frequency ventilation and finally ECMO as a last resort, have been used. Attempts at management of PPHN have of necessity aimed at reduction in pulmonary pressure to stop the shunting. Drug therapy with tolazoline results in undesirable alteration of systemic blood pressure and hence the drug has not been popular in neonates. Hyperventilation by causing high PaO_2 has been shown to lower pulmonary pressure though marginally and inconsistently. Inhaled nitric oxide a potent pulmonary vascular dilator is useful but requires special equipment. Extracorporeal-membrane oxygenation — (ECMO) has also been used where it is available but the advent of nitric oxide inhalation removed the need for ECMO in management of PPHN.

Pulmonary Vasodilators

Inhaled nitric oxide and ECMO improves oxygenation and can be tried when conventional modalities have failed. However availability of both these modalities is limited to only a few centers in the developing world.

More and more reports are getting published regarding the use of Sildenafil[19] (VIAGRA by pfizer) for use in PPHN both by oral route and intratracheal route.Sildenafil was originally marketed for treatment of male sexual dysfunction which remains its main use. It is a potent oral medication that is a specific inhibitor of phosphodiesterase – 5 (PDE – 5), an enzyme that hydrolyses cyclic guanosine monophosphate (cGMP). Cyclic - GMP mediates pulmonary vasodilation possibly as a second messenger for endogenous nitric oxide production. PDE – 5 is in high concentration in the lungs. It's inhibition by sildenafil results in a sustained rise in cGMP and subsequent pulmonary vasodilatation. The effect of sildenafil on pulmonary vasculature appears to be independent of the underlying cause of the raised pulmonary pressure. Due to this, it may be useful in a range of settings of pulmonary hypertension including PPHN.[20-22]

In animal study in 18 Piglets pulmonary hypertension was induced by endotracheal instillation of human meconium, 6 piglets subsequently received an infusion of intravenous sildenafil for 2 hours, 6 received inhaled nitric oxide for 2 hours, and 6 control animals received no additional intervention.[23] Meconium aspiration increased pulmonary vascular resistance by 70 percent, and increased oxygenation index by over 100 percent. Pulmonary vascular resistance remained elevated for the remainder of the study period in control animals. Inhaled nitric oxide reduced the pulmonary vascular resistance by 40 percent after 2 hours of treatment; intravenous sildenafil completely reversed the increase in pulmonary vascular resistance within 1 hour of commencing the infusion. Neither agent had an effect on systemic hemodynamics. Sildenafil also increased cardiac output by 30 percent, but while doing so did not adversely influence oxygenation.

Intravenous sildenafil is a selective and highly effective pulmonary vasodilator, which is at least as effective as inhaled nitric oxide, in this model of neonatal persistent pulmonary hypertension.

In one case report (2 new borns) from south Africa,[24] 0.5 mg/kg/six hourly and had remarkably good response without increasing the dose. The therapy was a last resort when other available means had apparently failed or were inappropriate. The pulmonary pressure reduced rapidly in two to three days and remained normal after withdrawal of the drug. The use of sildenafil removes the need for sophisticated equipment such as a ventilator or infusion pumps that are in short supply in developing countries. It is not possible from these cases to ascertain whether the use of sildenafil had any undesirable side effects. While sildenafil is an expensive drug even by developed country standards, its use removes the need for extra expense in sophisticated equipment hence may be useful in developing countries if it is used for a brief period in the neonate.

There is a role for the use of surfactant in intubated infants with MAS. A Cochrane Review showed that surfactant administration reduced the severity of respiratory illness and decreased the requirement for ECMO.[25] A very recent multicentric randomized study[26] showed improved oxygenation in babies who received surfactant . The study used porcine surfactant (Curosurf) at 200 mg/kg followed by 200 mg/kg, 100 mg/kg and 100 mg/kg were given at 6-12 hourly intervals, maximum of 4 doses if oxygenation index deteriorated >2 from baseline.

As Surfactant is very expensive another option is the use of diluted surfactant for broncho-alveolar lavage. Although this at present is considered an experimental therapy, case reports of benefit have been reported. A recent study[27] used 15 ml/kg of diluted porcine surfactant (5.3mg phospholipids per ml) in 2.5 ml aliquots in 8 babies intubated with severe ARDS due to MAS . Chest X-ray improvement was seen in all cases along with improved oxygenation. No major adverse effects were seen.

Broad spectrum antibiotic cover is appropriate until the possibility of infection is ruled out. Close monitoring of vitals is mandatory.

Blood counts should be done routinely. Thrombocytopenia may be an early marker of DIC. If there is a clinical indication, or a history suggestive of significant asphyxia, coagulation profile should be checked. Electrolytes must also be monitored as there is risk of hyponatremia due to inappropriate ADH. Hyperkalemia may be associated with deranged renal function. Hypocalcemia may be associated with birth asphyxia.

Theoretically steroids may be beneficial in MAS as they reduce inflammation. A recent Cochrane review however has shown no benefit in using steroids.[28] With growing concern about the effect of steroids on the developing brain its use is no longer recommended.

Outcome

Mortality associated with MAS has been gradually declining over the years. However 4-12 percent of babies continue to succumb to their illness. These babies are usually the ones with severe hypoxia, PPHN and airleaks. Few babies also suffer mortality and morbidity related to neurological and renal sequelae of severe birth asphyxia.

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CHAPTER

Acute Respiratory Failur

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GENERAL CONSIDERATIONS

Acute respiratory failure continues to be a major cause of morbidity and mortality in children and adults. If defined as the necessity for endotracheal intubation and mechanical ventilation, the incidence in Europe is 78-88 cases per 100,000 inhabitants per year.[1,2] There are no community-based studies in India. However, respiratory illnesses contribute to a major proportion of pediatric intensive care unit admissions in India that varies from 19.7–33.3%.[3-5]

The frequency of acute respiratory failure is higher in infants and young children than in adults because of the developmental differences that influence their susceptibility to respiratory failure. The infant, for the first few months of life, is primarily an obligate nose breather. This results in limitation of the ability to convert to oral breathing in those born with choanal atresia or stenosis. A relatively large tongue with relatively undeveloped mandible in an infant has the potential to obstruct the airway particularly if the size of the tongue is further increased as with a hemangioma or in a child with Down Syndrome or hypothyroidism. In contrast to those of adults, the subglottic region (the cricoid cartilage) being the narrowest part of a child's upper airway, is predisposed to edema from infection (croup) or mechanical trauma (endotracheal intubation or bronchoscopy). In general, airways are small in children below 5 years of age making them more vulnerable to increased airway resistance even by a small degree of obstruction due to bronchospasm or mucosal swelling resulting from viral infections of the lower airway. In addition, th relative weakness of cartilaginous support in infan compared with that of adults may lead to dynami compression of the trachea in conditions associate with high expiratory flow rates and increased airwa resistance.[6]

The compliant chest wall in infants and youn children makes it vulnerable to distortion in the forn of paradoxical inward motion of the rib cage o inspiration resulting from the negative pressur created by the downward movement of the diaphragm. This constitutes wasted work of breathin which has an enormous energy cost[7] and is noted a chest wall retractions on physical examination of th infant or a small child with respiratory distress.

The smaller alveolar size of the infant not onl predisposes to alveolar collapse but also leads t decreased diffusion surface available for ga exchange. Unlike adult lungs, the inability to allow ventilation distal to an obstructed airway by les developed pores of Kohn (interalveolar channels), Lambert's channels (bronchiole-alveolar channels) and interbronchiolar channels makes the infant and young child at increased risk for atelectasis or emphysematous changes and consequent ventilation/perfusion mismatching.

Definition

Simply stated, respiratory failure can be defined as a clinical state in which the respiratory system fails to meet the metabolic demands of the body for oxygenation and removal of carbon dioxide from the pulmonary circulation. Type 1 respiratory failure is diagnosed when the patient loses the ability to provide sufficient oxygen to the blood leading to hypoxemia, arbitrarily defined as a partial pressure of arterial oxygen (PaO_2) less than 60 mmHg. Type 2 respiratory failure occurs when the patient is unable to adequately ventilate which leads to hypercarbia and hypoxemia. A partial pressure of arterial carbon dioxide ($PaCO_2$) greater than 50 mmHg is frequently quoted to define type 2 respiratory failure. It is clear that hypercarbia is always associated with hypoxemia, whereas type 1 (hypoxemic) respiratory failure may be associated with a normal or low $PaCO_2$.

Respiratory failure is classified as acute when it develops over minutes or days and can be rapidly lethal. Chronic respiratory failure develops over a longer period of time and exists when gas exchange abnormalities persist past one month[8]. It is characterized by certain degree of metabolic compensation with an elevated plasma bicarbonate level to restore the pH close to normal in spite of persistently elevated $PaCO_2$.

Pathophysiology

Normal respiration may be divided into the following steps:

1. Ventilation, the exchange of respiratory gases between the atmosphere and lungs.
2. Pulmonary perfusion, the flow of mixed venous blood through the pulmonary circulation to the alveolar capillaries and the return of oxygenated blood from the capillaries to the left atrium .
3. Pulmonary gas exchange, the transfer of oxygen and carbon dioxide across the alveolar – capillary membrane in the lungs.
4. Gas transport and uptake, the conveying of arterial blood from the left ventricle to the peripheral tissues, which extract oxygen and release carbon dioxide for transport back to the right atrium.

Based on these normal functions of the respiratory system, the pathophysiology of respiratory failure can be discussed as follows:

1. **Failure of Ventilation:** The ventilatory function of the respiratory system is dependent on an intact respiratory pump which consists of feedback mechanism comprising of sensors (chemoreceptors and lung and airway receptors), controllers (cerebrum , brain stem and spinal cord) and effectors (chest wall, muscles of respiration). Failure of the respiratory pump leading to hypoventilation is a common reason for ventilatory failure leading to hypercapnia (Table 20.1).

Table 20.1: Common causes of ventilatory failure in children

Site of abnormality	*Examples*
Central control abnormality	CNS infections – meningitis, encephalitis Encephalopathies – hypoxic encephalopathy Drug overdose – sedatives, anesthetics Traumatic brain injury Stroke Sleep apnea
Airway obstruction	
Extrathoracic	
Acquired lesions	Infections – laryngotracheobronchitis, Ludwig angina, retropharyngeal abscess, peritonsillar abscess, Traumatic causes – post-extubation croup, foreign body aspiration, thermal burns Other causes - hypertrophic tonsils, adenoids
Congenital lesions	Craniofacial anomalies, choanal atresia, laryngomalacia, tracheomalacia, subglottic stenosis, web or cyst
Intrathoracic-extrapulmonary	Vascular ring, pulmonary sling, mediastinal mass, bronchogenic cyst, foreign body
Chest wall restriction	Diaphragm eventration, diaphragmatic hernia, kyphoscoliosis, flail chest, massive ascites
Respiratory muscle paralysis	Guillain-Barre syndrome, poliomyelitis, post-diphtheric, spinal cord trauma, hypokalemia, hypomagnesemia, hypophosphatemia, muscular dystrophy, spinal muscular atrophy, botulism Respiratory muscle fatigue following severe respiratory distress

In addition, hypoventilation very commonly results from respiratory muscle fatigue which occurs when the energy demands of the overworked respiratory muscles cannot be met. The increased work of breathing results from abnormal lung mechanics as seen with decreasing pulmonary compliance and/or increasing airway resistance.[9] Pulmonary compliance refers to the volume of gas that can move into the lung for each unit of pressure change. Thus compliance = $\Delta V/\Delta P$ where ΔP is the change in pressure required and ΔP is the volume produced. Conditions such as pneumonia, atelectasis, acute respiratory distress syndrome (ARDS), large pleural effusions and tension pneumothorax decrease the pulmonary compliance where as tense ascites,[10] obesity and vigorous respiratory muscle contraction lead to a fall in chest wall compliance. As opposed to these examples of restrictive respiratory disease, iatrogenic reasons such as use of endotracheal tube (even appropriately sized),[11] secretions or post-extubation airway obstruction in addition to disease such as bronchiolitis or asthma may be responsible for obstructive causes of increased work of breathing. Lower airway obstructive diseases cause hypercapnia relatively late in the course of the disease because of compensatory hyperventilation leading to CO_2 washout.

As mentioned earlier, significant hypercapnia is always associated with hypoxemia unless the patient receives supplemental oxygen, since increased alveolar carbon dioxide dilutes the available oxygen in the lungs. This is represented by the alveolar air equation:

$$PAO_2 = PiO_2 - PaCO_2/R$$

where P_AO_2 is the partial pressure of oxygen in the alveoli, P_IO_2 is the partial pressure of inspired oxygen and R is the respiratory quotient.

Since the lung function is unimpaired in hypoventilation, the difference between the alveolar PO_2 (PAO_2) and the arterial PO_2 (PaO_2), also known as the alveolar to arterial gradient [$P(A\text{–}a)O_2$] or alveolar–arterial PO_2 difference [$A\text{–}a\ DO_2$] is relatively small. It follows that if the $AaDO_2$ is found to be within normal limits, hypoxemia is entirely due to hypoventilation and not due to pulmonary gas exchange problems.

2. **Impaired Pulmonary Perfusion:** Impairment of blood flow to alveoli results in increased "dead space" in the lungs. This problem is seen most frequently with pulmonary emboli, a low cardiac output state and obliteration of pulmonary vasculature in certain lung diseases. Pulmonary embolism, although uncommon in pediatric population, may result in a very rapid deterioration of oxygenation without gross impairment of ventilation. It should be suspected in (1) cases involving abdominal, pelvic or lower extremity trauma (2) older and obese children that are immobile, and (3) children with increased susceptibility to venous thrombosis, such as those with nephrotic syndrome, burns, autoimmune diseases, and protein S, C, or antithrombin-3 deficiencies.
3. **Ventilation–perfusion (V/Q) imbalance or mismatch:** It is the relative distribution of ventilation and perfusion that is critical to effective oxygenation. Ventilation must take place where perfusion does and perfusion must occur in areas of good ventilation. When considering ventilation and perfusion, there can be four types of alveolar–capillary units. If ventilation and perfusion are normal, the unit is normal. If there is ventilation without perfusion ($V/Q = \infty$), the unit is considered to be dead space. If there is perfusion without ventilation ($V/Q = 0$), the unit is considered to be a pure (right–to–left) shunt. If there is neither ventilation nor perfusion, the unit is silent.

Ventilation/perfusion inequality is the most commonly encountered cause of hypoxemia. The commonly seen conditions causing hypoxemia due to V/Q mismatch are pneumonia, pulmonary edema, asthma, bronchiolitis, bronchopulmonary dysplaxia and acute respiratory distress syndrome (ARDS).

The reason why in spite of the presence of both high and low V/Q mismatch in lung diseases, the net result is always hypoxemia is the sigmoidal shape of the oxyhemoglobin dissociation curve. At the flat top portion of the oxyhemoglobin dissociation curve at which the hemoglobin is already fully saturated, an additional increase in PaO_2 from areas of high V/Q ratio can not further increase the oxygen saturation where as decreased PaO_2 from low V/Q areas significantly decreases the oxygen saturation of hemoglobin because of the steep gradient of the curve (Fig. 20.1).

Poor ventilation of a given lung unit can be compensated for by raising the oxygen concentration of the inspired gas it receives. The response to oxygen supplementation for V/Q imbalance depends upon the distribution of the abnormal V/Q units contributing to the problem.[12]

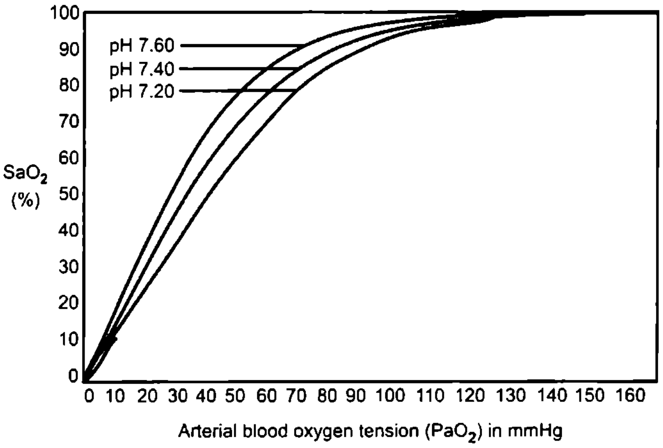


Fig. 20.1: Oxyhemoglobin dissociation curve. Acidosis causes a rightward shift of the curve decreasing the affinity of hemoglobin for oxygen (increased P50). Alkalosis causes a leftward shift of the curve increasing the affinity of hemoglobin for oxygen (decreased P50)

Arterial PO_2 rises linearly in lungs characterized by even a large number of lung units with mild V/Q impairment, whereas very high fraction of impaired oxygen (FiO_2) may be necessary to raise arterial PO_2 when V/Q abnormality is severe. At the same time, using high FiO_2 may paradoxically result in increased V/Q mismatching because of the replacement of unabsorbable nitrogen in the alveolar unit by absorbable oxygen causing collapse of these units (absorption atelectasis).[13]

The importance of matching of ventilation with perfusion is such that several mechanisms have developed to effect pulmonary microvascular regulation. Local acidosis, such as that existing in poorly ventilated areas tends to vasoconstrict the pulmonary arterial microvessels. Hypoxic pulmonary vasoconstriction is a much more powerful mechanism to divert deoxygenated blood from poorly ventilated units, which for most individuals is a well developed protection against perfusing underventilated areas.[14] Inflammatory conditions, however, may inhibit hypoxic vasoconstriction, worsening arterial hypoxemia, as does hypocapnic alkalosis.[15]

Developmental difference in V/Q matching: The normal term newborn has a significantly lower PaO_2 than that of the adult, because of increased V/Q mismatch resulting from persistent fetal vascular channels and atelectatic areas of the lung.[16] At 24 hours of life, the mean PaO_2 is 70 mmHg, rising up to 90 mmHg between the ages of 1 month to 2 years, where as beyond the age of 7 years, it does not vary with age and remains constant at the adult value of approximately 95 –100 mmHg.[17]

4. **Impaired gas transfer across the alveolar – capillary membrane:** Diffusion impairment by itself is never the major cause of respiratory failure primarily because the transfer of oxygen from alveolus to hemoglobin usually requires only a brief time for completion–somewhat less than the normal transit time of the erythrocyte through the capillary.[18] However, transudation of fluid across the alveolar capillary membrane, with resultant pulmonary, interstitial and alveolar edema, is a major cause of respiratory failure. Several types of insults may disrupt alveolar – capillary membrane integrity, and the resultant pulmonary edema in the face of the normal hydrostatic pressure causes acute respiratory distress syndrome. Another extremely rare reason for diffusion impairment in children is increase in the thickness of the alveolar–capillary membrane as seen in pulmonary fibrosis.

   Diffusion is virtually never a problem with carbon dioxide since the diffusion coefficient of carbon dioxide is 20 times that of oxygen. Carbon dioxide normally diffuses through the respiratory membrane so rapidly that the average difference between the PCO_2 in the pulmonary capillary blood and in alveoli is less than 1 mmHg.

5. **Impaired gas transport and uptake by the tissues:** Impaired oxygen transport as seen in anemia, carbon monoxide poisoning, cardiogenic shock and failure of tissue oxygen extraction, for example in cyanide poisoning result in inadequate oxygenation of the tissues, but are traditionally not considered under the term respiratory failure and therefore will not be considered further.

Oxygen delivery and oxygen consumption: A basic understanding of the concept of oxygen delivery (DO_2), oxygen consumption (VO_2) and oxygen extraction is necessary for rational management of children with respiratory failure. DO_2 is the product of cardiac output (Q) and arterial oxygen content (CaO_2):

$$DO_2 = Q \times CaO_2$$

The oxygen content of arterial blood (CaO_2) is determined primarily by the hemoglobin level and the oxygen saturation of hemoglobin. Since each gram of hemoglobin carries 1.34 ml of oxygen when fully saturated, by multiplying 1.34 with hemoglobin concentration and the arterial oxygen saturation (SaO_2), the amount of oxygen bound to hemoglobin can be calculated. The small amount of dissolved oxygen in plasma (oxygen has a solubility of only 0.003 ml/dl blood/PaO_2 at 37° C) is added to this to find out the CaO_2. Thus, the equation for CaO_2 calculation is:

$$CaO_2 = [1.34\,(mLO_2/\,g\,Hb) \times Hb\,(g/\,dL) \times SaO_2/100] + [PaO_2\,(mmHg) \times 0.003\,(ml\,O_2/dL/\,mmHg]$$

Oxygen consumption (VO_2) is the product of arterial and venous oxygen content difference ($C_{a\text{-}v}O_2$) and cardiac output:

$$VO_2 = Q \times C_{a\text{-}v}O_2$$

Resting VO_2 in the newborn is about 6 ml/kg/min. as compared to that in adults in whom it is about 3/ml/kg/min. The portion of DO_2 which is consumed by the tissues is called the oxygen extraction ratio and is normally 0.25 approximately.[19] When DO_2 falls, the extraction ratio increases to maintain a constant VO_2; however, below a critical DO_2, oxygen extraction cannot increase further and VO_2 starts falling. In anesthetized adults, this critical oxygen delivery threshold corresponds to a DO_2 of 300 to 330 ml/min/m^2.[20] The critical oxygen delivery threshold is raised substantially in patients with ARDS and systemic inflammatory response syndrome (SIRS), thus increasing their requirement for a higher level of DO_2 to meet their VO_2 requirements (Fig.20.2).[21]

Another important factor governing tissue oxygen uptake is the readiness of the hemoglobin to release oxygen to the tissues. This depends on the position of the oxygen–hemoglobin dissociation curve and by the partial pressure of oxygen at which half the hemoglobin is saturated, the P_{50}. When the temperature and PCO_2 rise and the pH declines, as occurs when there is active tissue metabolism, the dissociation curve is shifted to the right and the P_{50} increases, i.e., oxygen is readily released. Conversely, when the temperature and PCO_2 fall and the pH rises, as occurs when tissue metabolism is low, the dissociation curve is shifted to the left and the P_{50} decreases, thus decreasing the oxygen release (Fig.20.1).

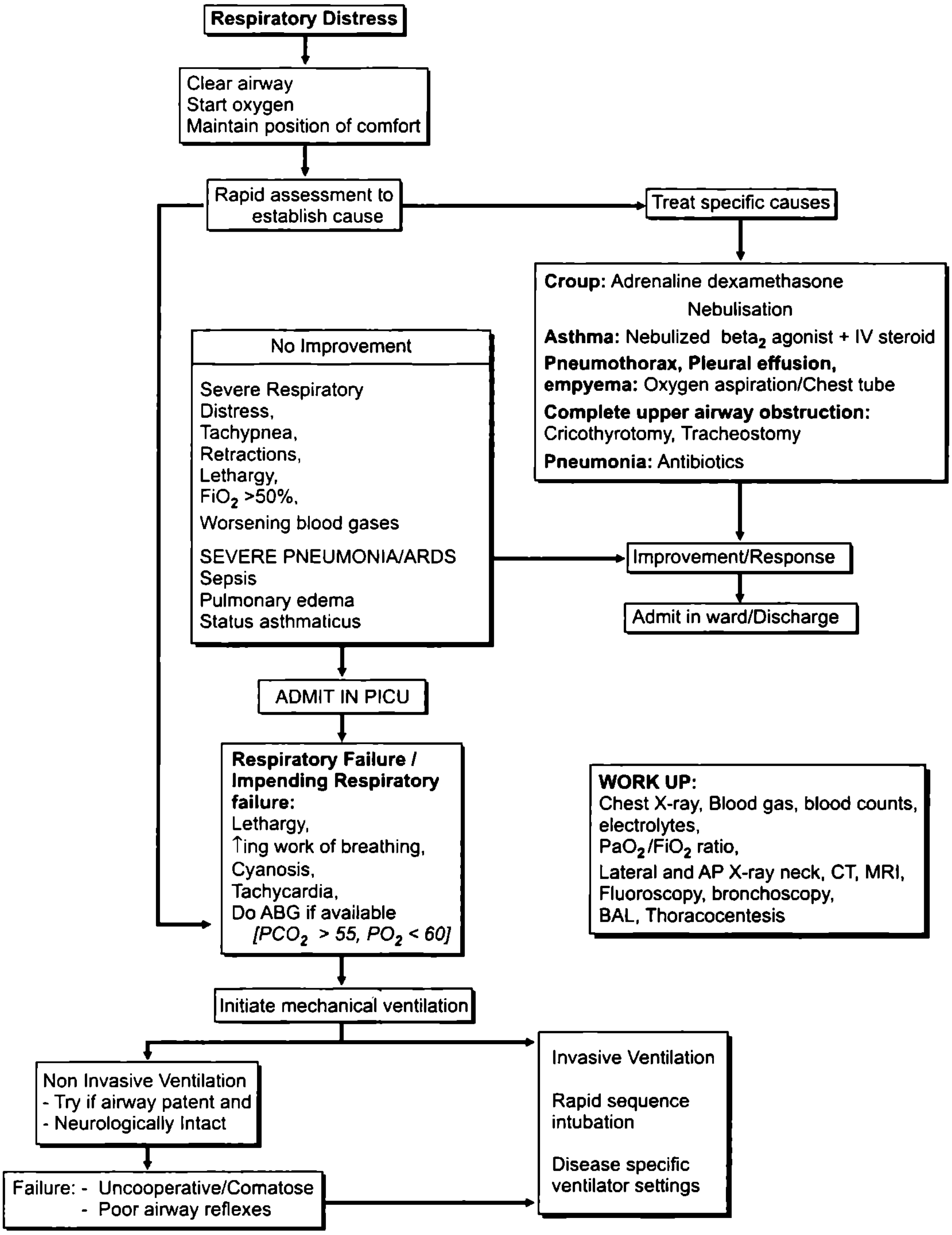
Clinical Evaluation of a Child with Impending Respiratory Failure (Flow chart 20.1)

Conventional pediatric teaching emphasizes on etiologic diagnosis. Undoubtedly, the precise etiologic diagnosis is necessary, but in acute or emergency care, intervention has to be immediate; it cannot wait for establishment of the diagnosis. For this reason, a five point quick clinical assessment is invaluable to identify the degree of alteration in the child's respiratory physiological status and to identify any rectifiable life threatening cause of poor gas exchange:

1. **State of consciousness:** Lethargy, confusion, agitation may be signs of hypoxemia and hypercarbia. Decreased level of activity and cry may be indicative of impending respiratory failure in an infant with respiratory distress.
2. **Assessment of the presence and probable site of airway obstruction:** One should quickly assess whether the airway is patent or obstructed and if obstructed, the probable site of airway obstruction in child with suspected respiratory failure. Signs such as inspiratory retraction, stridor, wheezing, grunting along with a worried, restless general appearance are suggestive of increasing airway obstruction. Impending collapse due to severe airway obstruction is suggested by the following signs :
    - Markedly decreased respiratory effort, decreased stridor and breath sounds.
    - Restless, distracted activity, decreased consciousness level, hypotonia.
    - Cyanosis or extreme pallor.

   Quick assessment of the site of obstruction is helpful to select appropriate intervention(Table 20.2)
3. **Assessment of breathing and work of breathing** Assessment of breathing helps to judge the degree of derangement in gas exchange. This is done by assessment of minute ventilation by clinical estimation of tidal volume and respiratory rate . The presence of poor chest excursions, diffusely

Flow chart 20.1: Manage respiratory distress


Respiratory Distress
Clear airway
Start oxygen
Maintain position of comfort
Rapid assessment to establish cause
Treat specific causes
Croup: Adrenaline dexamethasone Nebulisation
Asthma: Nebulized beta$_2$ agonist + IV steroid
Pneumothorax, Pleural effusion, empyema: Oxygen aspiration/Chest tube
Complete upper airway obstruction: Cricothyrotomy, Tracheostomy
Pneumonia: Antibiotics
No Improvement
Severe Respiratory Distress,
Tachypnea,
Retractions,
Lethargy,
FiO$_2$ >50%,
Worsening blood gases
SEVERE PNEUMONIA/ARDS
Sepsis
Pulmonary edema
Status asthmaticus
Improvement/Response
Admit in ward/Discharge
ADMIT IN PICU
Respiratory Failure / Impending Respiratory failure:
Lethargy,
↑ing work of breathing,
Cyanosis,
Tachycardia,
Do ABG if available
[PCO$_2$ > 55, PO$_2$ < 60]
WORK UP:
Chest X-ray, Blood gas, blood counts, electrolytes,
PaO$_2$/FiO$_2$ ratio,
Lateral and AP X-ray neck, CT, MRI, Fluoroscopy, bronchoscopy,
BAL, Thoracocentesis
Initiate mechanical ventilation
Non Invasive Ventilation
- Try if airway patent and
- Neurologically Intact
Failure: - Uncooperative/Comatose
- Poor airway reflexes
Invasive Ventilation
Rapid sequence intubation
Disease specific ventilator settings

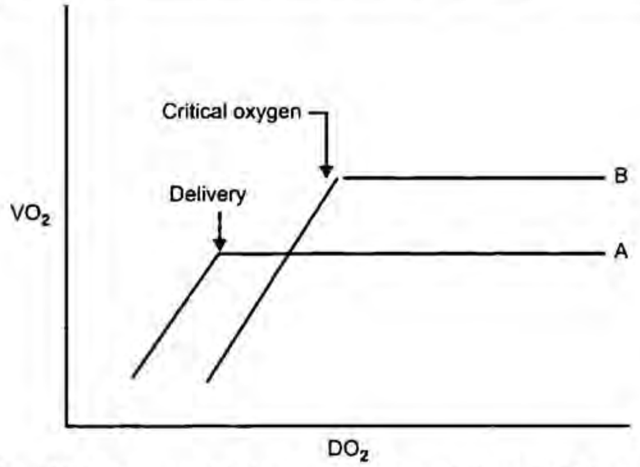


Fig. 20.2: Relationship between oxygen delivery (DO_2) and oxygen consumption (VO_2).[21] (A) In normal individuals, oxygen consumption falls only when oxygen delivery becomes critically low. (B) Critical oxygen delivery threshold is substantially raised in patients with ARDS/ SIRS so that a higher level of DO_2 is necessary to meet the VO_2 requirements

diminished breath sounds and slow, irregular respiration is indicative of significant hypoventilation.

On the other hand, a markedly increased respiratory rate with nasal flaring, accessory muscle use and marked suprasternal, intercostal and subcostal retractions indicate very significant increase in the work of breathing. Since this state of compensation (respiratory distress) may rapidly and unpredictably convert into a decompensated state (respiratory failure) in children because of their limited ability to compensate., early anticipation of respiratory failure and intervention by intubation and mechanical ventilation, if indicated, is essential.

Table 20.2: Clinical assessment of site of airway obstruction*

	Site of obstruction		
Sign	*Extrathoracic airway obstruction*	*Intrathoracic airway obstruction*	*Intrapulmonary airway obstruction*
Tachypnea	+	+	++
Retractions	++++	++	++
Stridor	++++	++	-
Wheezing	+	+++	++++
Grunting	+	+	++

*Reproduced from: Sarnaik AP. Evaluation of a child in respiratory distress: a clinical approach. In: Abstracts of the 4th National Critical Care Congress, Pune, Jan 1998, ISCCM, 11 B, 6-8.

4. **Cyanosis:** Cyanosis is a fairly late and unreliab sign as it is influenced by skin perfusion an hemoglobin concentration and is subject to a l of subjective error in assessment. Thus hypox mia should be suspected in children with resp ratory disease before the appearance of cyanos in accordance with signs described above.
5. **Heart rate:** Tachycardia, though nonspecific, an important accompaniment of hypoventilatio and hypoxia. However, if bradycardia occurs i an acutely ill infant or child, it is most ofte suggestive of impending cardiorespiratory arre due to profound hypoxemia and acidosis.

Workup

Workup of children with acute respiratory failur should follow initial stabilization of the patient. Th relevant investigations for a particular patient hav to be individualized and prioritized in accordanc with the underlying pathophysiology, probabl diagnosis based on history, physical examination an the results of ongoing monitoring of the patient.

Lab/Bedside Studies:

1. **Arterial blood gas analysis** can be used to defin acute respiratory failure; arbitrarily, definitio includes a $PaCO_2$ greater than 50 mmHg and PaO_2 less than 60 mmHg as mentioned in th Section on 'Definition'.
2. **Complete blood count** polycythemia suggest chronic hypoxemia.
3. **Electrolyte estimation** hypokalemia, hypocalcemia and hypophosphatamia can impair muscl contraction and may be a contributor to acut respiratory failure.
4. **Calculation of the alveolar-arterial oxygen difference [(A-a)DO_2].** This value is an index of the efficiency of gas exchange by the lungs. As mentioned in the Section on 'Pathophysiology', the alveolar air equation calculates the alveolar PO_2 (PAO_2) by the relationship between the PO_2 in inspired gas (PiO_2), the $PaCO_2$ and the respiratory quotient (R):

$$PAO_2 = P_iO_2 - (PaCO_2/R),$$

where R is the flow of CO_2 molecules across the alveolar membrane per minute, divided by the flow of O_2 molecules across the alveolar membrane/min. Normally, the body produces approximately 200 ml of CO_2/min. and consumes approximately 250ml of oxygen/min.; therefore, R is 0.8. Different fuel sources have different R values; for carbohydrates, R is 1; for proteins, R is 0.8; and for fat, R is 0.7. Substituting the value of R as 0.8:

$$PAO_2 = PiO_2 - PaCO_2/0.8$$

or

$$PAO_2 = PiO_2 - PaCO_2 \times 1.25$$

The value of PiO_2 can be obtained by subtracting the pressure of water vapour (which is 47 mmHg at body temperature of 37°C when air is fully saturated) from the atmospheric pressure of 760 mmHg at sea level and multiplying this by 0.21. Thus $PiO_2 = (760-47)\ 0.21 = 149.7$, or about 150. Substituting the obtained $PaCO_2$ value in the alveolar air equation gives the value of PAO_2 (Fig. 20.3)

In children, (A-a) DO_2 is normally 5-10 mmHg in room air (It is caused by venous admixture from normal anatomic right-to-left shunts including the bronchial circulation, thesbian veins, and small arteriovenous anastomoses).

The (A-a) DO_2 is widened when a V/Q mismatch, right-to-left shunt or diffusion defect is the mechanism producing hypoxemia in contrast to hypoventilation as the cause of hypoxemia. Interpretation of values of (A-a) DO_2 should be done with caution at higher oxygen concentrations. The normal (A-a) DO_2 widens with higher fractions of inspired oxygen. This value may reach up to 70 mmHg when PAO_2 exceeds 350-450 mmHg and then decreases at a higher PO_2 so inscribing a bell-shaped curve. Thus between the two extremes of inhaled FiO_2 (0.21 and 1.0), the expected (A-a) DO_2 level even in normal subject is difficult to predict, and there is no reliable reference values for patients with intermediate levels of FiO_2.

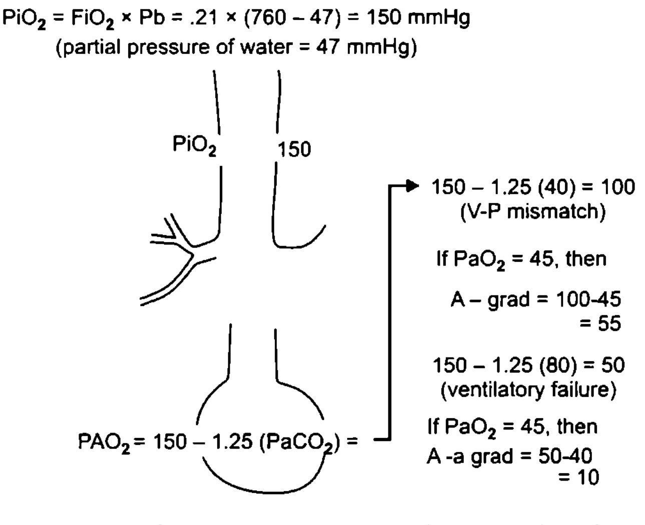


Fig. 20.3: Schematic diagram showing examples of calculation for alveolar-arterial gradient

1. **The PaO_2/FiO_2 ratio** is a commonly used indicator of impairment of oxygenation. Normally this ratio is $(100/0.21) = 500$. A PaO_2/FiO_2 ratio of less than 200 correlates with a shunt fraction of > 20% (see 'Determination of intra-pulmonary shunt fraction').
2. **The oxygenation index** also takes into account the mean airway pressure as a determinant of oxygenation and is a better indicator of oxygenation in mechanically ventilated patients. It is: Oxygenation index (OI)= Mean airway pressure (MAP) × $FiO_2 \times 100/ PaO_2$.
3. **Determination of dead-space volume to tidal gas volume (Vd/Vt)** Vd/Vt is based on the difference between $PaCO_2$ and the CO_2 in exhaled gas ($PeCO_2$). $PeCO_2$ is measured by collecting expired gas in a large collection bag and using an infrared CO_2 analyser to measure the PCO_2 in a sample of gas. In a normal lung the capillary blood equilibrates fully with the alveolar gas; therefore, the $PeCO_2$ approximates the $PaCO_2$. As the Vd/Vt increases, the $PeCO_2$ falls below $PaCO_2$. $Vd/Vt = (PaCO_2 - PeCO_2/PaCO_2)$.
4. **Determination of the intrapulmonary shunt fraction** The amount of physiologic shunting in the lung (or venous- arterial admixture) (Qs/Qt) is the most accurate and sensitive guide to the onset and progression of acute respiratory failure. Physiologic shunting in the lungs refers to that fraction of blood passing through the lungs without being oxygenated and is normally about 3% to 5% of the cardiac output.

The Qs/ Qt can be calculated from a modification of Berggren's formulae

$$Qs/Qt = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

where CcO_2 is the pulmonary capillary oxygen content, CaO_2 is the arterial oxygen content, and CvO_2 is the mixed venous (pulmonary artery) oxygen content.

Directly measuring the pulmonary capillary oxygen content (CcO_2) is difficult, thus it is calculated from the FiO_2 concentration of hemoglobin and the estimated alveolar PAO_2 by the following formula:

$$CcO_2 = [Hb]\ (1.34) + (PAO_2)\ (0.003)$$

The arterial oxygen content (CaO_2) and mixed venous oxygen content (CvO_2) are calculated from the hemoglobin and their respective oxygen saturations and PO_2 as follows:

$$CaO_2 = [Hb]\ (1.34)\ (SaO_2/\ 100) + (PaO_2)\ (0.003)$$
$$CvO_2 = [Hb]\ (1.34)\ (SvO_2/\ 100) + (PvO_2)\ (0.003)$$

where (Hb) is the hemoglobin concentration, SaO_2 and SvO_2 are the arterial and mixed venous oxygen saturations respectively, and PaO_2 and PvO_2 are the arterial and mixed venous oxygen tensions respectively.

For calculation of CvO_2, mixed venous samples from pulmonary artery are preferable to those obtained from central venous pressure catheters. However, central venous blood can be used to provide a reasonable estimate of shunting present if the cardiac output is normal.

Imaging Studies:

5. **Lateral and AP radiographs of the neck** can depict a radio opaque foreign-body or a soft tissue structure encroaching airway lumen.
6. **Chest X-rays** are very useful to evaluate for abnormalities that require immediate intervention (e.g. malpositioned endotracheal tube, pneumothorax.). Common findings associates with respiratory failure include: focal or diffused pulmonary disease (e.g. pneumonia, ARDS), bilateral hyperinflation (e.g. asthma), asymmetric lung expansion suggesting a bronchial obstruction, pleural effusion, cardiomegaly etc.
7. **Chest CT:** It can sometimes further define radiodensities due to vascular, pleural, interstertial, or airway lesions.
8. **Airway CT scanning, MRI, or angiography** can be used to differentiate deep tissue structure, bone lesions and vascular abnormalities from one another. CT angiography may be done to rule out pulmonary embolism if indicated.
9. **Fluroscopy** is valuable to evaluate the movement of the diaphragms and dynamic obstructive lesion of both the extra- and intrathoracic airway.
10. **Ventilation-perfusion scanning** can predict a probability of V/Q mismatch as in pulmonary embolism.

Diagnostic Procedures

Additional diagnostic procedures may be indicated for confirmation of precise etiologic diagnosis, e.g.:

11. **Bronchoscopy** Fiberoptic or rigid bronchoscopy may be needed to assess the airway for anatomic abnormalities and foreign body.
12. **Broncho-alveolar lavage (BAL)** is done to identify a specific pulmonary pathogen; silver stain and bacterial, viral, fungal and AFB can be sent.
13. **Thoracentesis** for cytology, chemical analyses and cultures
14. **Lung biopsy** is indicated if other means of diagnosis do not reveal a pathogen
15. **EMG/NCV** may be needed to find out the etiology of neuromuscular weakness.
16. **Polysomnography or sleep studies** for obstructive or central sleep apnea

Principles of Treatment

Support of respiratory function of the child whose respiratory failure is imminent or already established, should be initiated instantly based on quick assessment as discussed in the foregoing sections and determination of the underlying etiology. While supporting the respiratory system and ensuring oxygen delivery to the tissues, an intervention specifically to correct the underlying conditions may be life saving. Examples of such interventions are: needle aspiration for tension pneumothorax, naloxone for narcotic associated hypoventilation, nebulized β-agonists and steroids for severe asthma episode, tracheotomy or cricothyroidotomy for complete or nearly complete airway obstruction and rapid sequence intubation for a plethora of conditions leading to acute respiratory failure.

Airway Management

The first decision is whether a tracheal intubation is needed. While unnecessary or too early intubation may expose the child to hazards of intubation and / or mechanical ventilation, unwarranted delays may result in complications associated with emergency intubation. Upper airway obstruction resulting in markedly compromised air movement, loss of protective airway reflexes such as coughing or gag reflex and apnea are an immediate threat to life and therefore establishment of an artificial airway by endotracheal intubation (usually) or tracheostomy (sometimes) or cricothyrotomy (rarely) is the most pressing immediate priority.

Lung and Respiratory Pump Support (Flow chart 20.2)

Oxygen Therapy: Prompt use of oxygen in acute respiratory failure is life saving. The reader is referred to chapter 43 for detailed discussion on oxygen therapy.

Indications for Admission to the PICU

Patients too unstable to be managed in ward
Severe respiratory distress, tachypnea and retractions
Oxygen requirement on the rise >50% to maintain oxyhemoglobin saturations above 90%.
Desaturation below 90% on highest flow of oxygen
Lethargic child
Arterial blood gas showing hypoxemia, hypercarbia or metabolic acidosis

Indications of Mechanical Ventilation

Indications are mainly clinical (blood gas though important but not absolutely necessary): paO_2 <55 mmHg or $paCO_2$ >60 despite 100% oxygen therapy.
Deteriorating respiratory status despite oxygen and nebulization therapy.
Anxious, sweaty lethargic child with deteriorating mental status Respiratory arrest (must be avoided at all cost)

Continuous positive airway pressure (CPAP): CPAP may be indicated if a lung disease results in severe oxygenation abnormalities such that an FiO_2 of more than 0.6 is needed to maintain a PAO_2 of more than 60 mmHg. Usually pressure between 3 and 10 cm of water are used. CPAP improves oxygenation by increasing the lung volume, redistribution of fluid from the alveoli and interstitium, increased ventilation in areas of low V/Q by opening up of atelectatic alveolar units and improved respiratory mechanics.

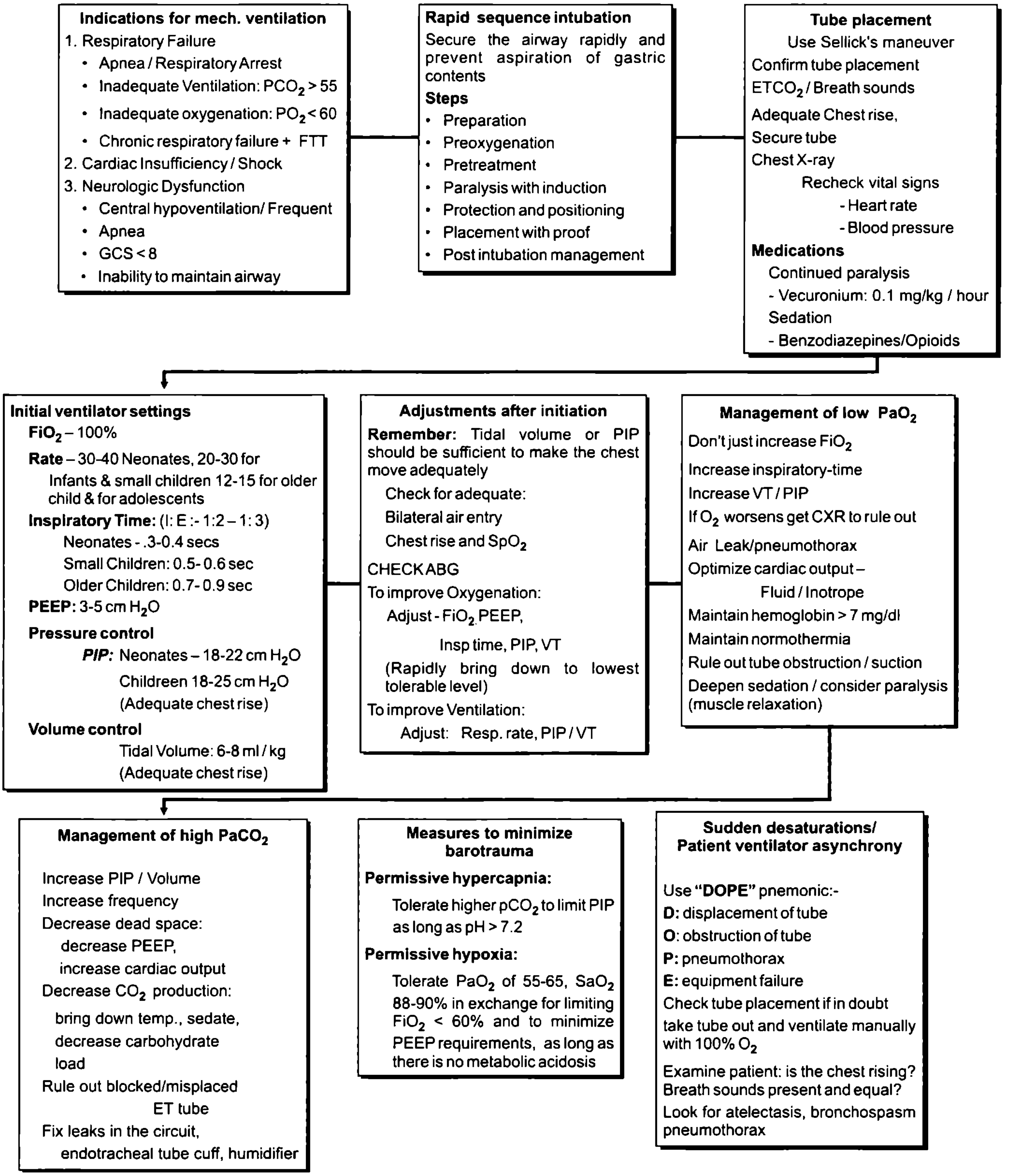
Positive pressure ventilation: Institution of positive pressure ventilation has been one of the most important advance in the care of children with acute respiratory failure. The objective of mechanical ventilation is to support the respiratory function until the time when specific interventions such as antibiotics for severe pneumonia are able to resolve the underlying pathological process that resulted in respiratory failure. Since mechanical ventilation is associated with many complications that at times may be worse than the condition for which it was instituted, the goal of mechanical ventilation should be to " take the patient off the ventilator as early as possible". The reader is referred to chapter on mechanical ventilation for a detailed discussion.

Adjunctive Therapies:

1. **Inhaled nitric oxide**- Meta-analysis of five randomized controlled trials for use of inhaled nitric oxide for acute hypoxemic respiratory failure in children and adults show some immediate benefit, up to 72 hours on oxygenation.[22] However, data is insufficient to determine the effects on ventilator-free days, length of intensive care and hospital stay and mortality.[22]
2. **Extracorporeal membrane oxygenation (ECMO)**- ECMO is a technique for providing life-support, in case the natural lungs are failing and are not able to maintain a sufficient oxygenation of the body's organ systems. ECMO technique was an adaptation of conventional cardiopulmonary bypass technique and introduced into treatment of severe acute respiratory distress syndrome in the 1970s.

   Ever since ECMO was introduced in the treatment, quite promising survival rates of 80% in 10,391 newborns with acute hypoxemic respiratory failure have been observed.[23] In the 1980s, the technology was adapted to pediatric and later on, in the 1990s to adult acute respiratory failure and cardiac failure. In 1996, Green et a presented the results of a retrospective multi center cohort analysis of 331 pediatric patient that showed reduction in mortality.[24] However with the introduction of new therapies, such a high frequency ventilation, the use of nitric oxide and improvement in conventional therapies, use of ECMO is on the decline.[25]

Flow chart 20.2: Respiratory failure-mechanical ventilation



Indications for mech. ventilation

1. Respiratory Failure
   - Apnea / Respiratory Arrest
   - Inadequate Ventilation: $PCO_2 > 55$
   - Inadequate oxygenation: $PO_2 < 60$
   - Chronic respiratory failure + FTT
2. Cardiac Insufficiency / Shock
3. Neurologic Dysfunction
   - Central hypoventilation/ Frequent
   - Apnea
   - GCS < 8
   - Inability to maintain airway

Rapid sequence intubation

Secure the airway rapidly and prevent aspiration of gastric contents

Steps

- Preparation
- Preoxygenation
- Pretreatment
- Paralysis with induction
- Protection and positioning
- Placement with proof
- Post intubation management

Tube placement

Use Sellick's maneuver

Confirm tube placement

$ETCO_2$ / Breath sounds

Adequate Chest rise,

Secure tube

Chest X-ray

Recheck vital signs

- Heart rate
- Blood pressure

Medications

Continued paralysis

- Vecuronium: 0.1 mg/kg / hour

Sedation

- Benzodiazepines/Opioids

Initial ventilator settings

FiO_2 – 100%

Rate – 30-40 Neonates, 20-30 for Infants & small children 12-15 for older child & for adolescents

Inspiratory Time: (I: E :- 1:2 – 1: 3)

Neonates - .3-0.4 secs

Small Children: 0.5- 0.6 sec

Older Children: 0.7- 0.9 sec

PEEP: 3-5 cm H_2O

Pressure control

PIP: Neonates – 18-22 cm H_2O

Childreen 18-25 cm H_2O

(Adequate chest rise)

Volume control

Tidal Volume: 6-8 ml / kg

(Adequate chest rise)

Adjustments after initiation

Remember: Tidal volume or PIP should be sufficient to make the chest move adequately

Check for adequate:

Bilateral air entry

Chest rise and SpO_2

CHECK ABG

To improve Oxygenation:

Adjust - FiO_2 PEEP,

Insp time, PIP, VT

(Rapidly bring down to lowest tolerable level)

To improve Ventilation:

Adjust: Resp. rate, PIP / VT

Management of low PaO_2

Don't just increase FiO_2

Increase inspiratory-time

Increase VT / PIP

If O_2 worsens get CXR to rule out

Air Leak/pneumothorax

Optimize cardiac output –

Fluid / Inotrope

Maintain hemoglobin > 7 mg/dl

Maintain normothermia

Rule out tube obstruction / suction

Deepen sedation / consider paralysis (muscle relaxation)

Management of high $PaCO_2$

Increase PIP / Volume

Increase frequency

Decrease dead space:

decrease PEEP,

increase cardiac output

Decrease CO_2 production:

bring down temp., sedate, decrease carbohydrate load

Rule out blocked/misplaced ET tube

Fix leaks in the circuit, endotracheal tube cuff, humidifier

Measures to minimize barotrauma

Permissive hypercapnia:

Tolerate higher pCO_2 to limit PIP as long as pH > 7.2

Permissive hypoxia:

Tolerate PaO_2 of 55-65, SaO_2 88-90% in exchange for limiting $FiO_2 < 60\%$ and to minimize PEEP requirements, as long as there is no metabolic acidosis

Sudden desaturations/ Patient ventilator asynchrony

Use **"DOPE"** pnemonic:-

D: displacement of tube

O: obstruction of tube

P: pneumothorax

E: equipment failure

Check tube placement if in doubt take tube out and ventilate manually with 100% O_2

Examine patient: is the chest rising? Breath sounds present and equal?

Look for atelectasis, bronchospasm pneumothorax

(PIP: peak inspiratory pressure, PCO_2: partial pressure of CO_2, PaO_2: partial pressure of oxygen, $ETCO_2$ end tidal CO_2 FTT: failure to thrive, SaO_2 arterial Oxygen saturation)

SPECIFIC DISORDERS LEADING TO ARF: IMPORTANT ISSUES IN DIAGNOSIS AND MANAGEMENT

Following clinical problems and their emergency management issues will be discussed

(a) **Upper airway obstruction**
(b) **Bronchiolitis**
(c) **Acute asthma**
(d) **Pneumonia**
(e) **Neuromuscular disorders**
(f) **ARDS**
(g) **Pneumothorax**

(a) *Upper airway obstruction:* Nasal and pharyngeal causes such as choanal stenosis or atresia will cause cyanosis at rest. Common symptom of upper airway obstruction is stridor in infancy.

Important causes of stridor include:

Laryngomalacia vocal cord paralysis, laryngeal web vascular ring tracheal stenosis airway hemangiomas, hypocalcemia, hypoparathyroidism.

In older child common infectious causes causing upper airway obstruction (signs and symptoms of hoarseness, drooling swallowing difficulty, stridor with or without respiratory distress) include:

Laryngotracheobronchitis
Epiglottitis
Diphtheria
Tonsillitis/peritonsillar abscess
Retro pharyngeal abscess
Bacterial tracheitis
Tracheobronchomalacia.

Other causes of upper airway obstruction should always be looked into such as airway foreign bodies, airway tumors ,post intubation stridor, subglottic stenosis.

Emergency department investigations and management:

Oxygen for all Patients and no Sedation

Is airway maintained? If stable airway: maintain position of comfort do not force to examine the airway and do not lay the child forcefully. Accompany child for portable soft tissue anteroposterior and lateral neck X-rays.

If unstable airway: Secure airway first in best possible location in controlled environment, i.e. operation theatre or the PICU with availability of emergency tracheostomy.

Once airway has been secured.

Give intravenous antibiotics and steroids as indicated: Ceftriaxone/Cefuroxime for tracheitis, peritonsillar abscess and epiglottitis. Adrenaline nebulisation and intravenous methylprednisone/dexamethasone for laryngotracheobronchitis and hypertrophic tonsills in infectious mononucleosis.

For angioedema subcutaneous adrenaline and intravenous dexamethasone is indicated.

(b) *Bronchiolitis:* Emergency management: Viral infection (common causes include Respiratory Syncytial Virus, Parainfluenza, Influenza, and Adenovirus) of lower respiratory tract in infancy causing airway inflammation,mucosal edema as well as bronchoconstriction leading to wheezing and severe expiratory obstruction leading to severe respiratory distress. Chest radiograph shows hyperinflation as well as perihilar infiltrates but no evidence of lobar consolidation.

Treatment remains symptomatic until acute phase is over in 24 to 48 hours. Endotracheal intubation and mechanical ventilation is rarely required.

Key Treatment Points

Oxygen

Airway humidification

Adrenaline and Salbutamol nebulisation seem to be beneficial although more evidence from clinical studies favors use of adrenaline nebulisation as compared to beta two agonists since airway edema seems to play greater role in causing lower airway obstruction.

Steroids have no role unless prior evidence of repeated wheezing with suspected asthma in older infants and children above one year of age. Antibiotics are unnecessary however get frequently used empirically due to fever accompanying this illness.

The condition, generally self limiting, has a good prognosis.

(c) *Acute severe asthma:(see chapter on asthma):* Asthma is characterized by inflammation, mucosal exudation and edema as well as reversible lower airway obstruction with bronchospasm,wheezing with respiratory distress precipitated by one or combination of several factors such as viral infection, allergens, exposure to cold environment, exercise induced or induced by use of non steroidal analgesics/antinflammatory agents. Eicosenoids, leukotriens and platelet aggregating factors are important inflammatory mediators leading to mucosal edema and bronchospasm.

Management in emergency department: History of eczema, allergies, food allergies, family history of asthma are important factors to enquire about.

Clinical evaluation should be quick to include sensorium,respiratory rate heart rate color accessory musce use breath sounds/wheezes, oxyhemoglobin saturation on pulse oximeter and peak expiratory flow rate if older patient.

lAP guidelines have been published in 2003
Oxygen in combination with nebulizer therapy with beta two agonists intermittent or continuously, and intravenous steroids remain the cornerstone of therapy in the emergency room. Rarely very severe cases with lethargy and exhaustion with impending respiratory arrest or respiratory arrest will require immediate endotracheal intubation and mechanical ventilation.

Non responders to nebulised beta agonists may require subcutaneous adrenaline, terbutaline, intravenous terbutaline, intravenous salbutamol intravenous magnesium sulphate intravenous Ketamine and rarely general anesthesia.

Treatment : phase i : first hour
Oxygen in combination with nebulizer therapy with beta two agonists intermittent or continuously,and intravenous steroids remain the cornerstone of therapy in the emergency room.Rarely very severe cases with lethargy and exhustion with impending respiratory arrest or respiratory arrest will require immediate endotracheal intubation and mechanical ventilation. Salbutamol 0.15 mg/kg/dose (minimum 2.5 mg) every 20 min for 3 doses with oxygen flow rate of 6 to 8 I/mm or 4 to 8 puffs of metered dose inhaler (MDI) and spacer every 20 minutes(10 to 20 puffs in one hour) If nebuliser/MDI not available, may use adrenaline 0.01 mg/kg (1:1000 solution) or up to 0.3 to 0.5 terbutaline every 20 miri for 3 doses in 1st hour subcutaneously. Systemic steroids prednisone 2 mg/kg/dose,methyl prednisone into 2 mg/kg/dose or hydrocortisone 10 mg/kg/dose may be used intravenously, In emergency, intramuscular route can also be used at the end of first hour.

Repeat assessment:
if good response as indicated by following parameters:
Decrease in heart rate, decrease in respiratory rate, pulsus paradoxus <10 mmHg
alert sensorium
Oxyhemoglobin saturation >90%
PEFR(peak expiratory flow rate) >70%
Consider discharge on beta 2 agonists, oral steroid 3 to 10 days.

If incomplete/ poor response: As indicated by following clinical parameters

1. Heart rate elevated
2. Shallow respirations
3. Altered sensorium/exhaustion
4. O_2 saturation <90%
5. PEFR <50% to <70%

Consider admission to hospital.

Indications for admission to pediatric intensive care unit and possible intubation and mechanical ventilation include:
Altered consciousness
Exhaustion
Respiratory arrest
Shallow respirations or $paCO_2$ >50 mmHg
Worsening or persistent hypoxia pa 0_2 <60 mmHg
worsening metabolic acidosis.
Patient with pneumothorax

Other treatment modalities available include intravenous terbutaline, intravenous salbutamol, intravenous magnesium sulphate, intravenous Ketamine and rarely general anesthesia with halothane, isoflurane and enflurane.

(d)*Acute respiratory distress syndrome(ARDS)/ Pneumonia:* Predominantly alveolar disease with respiratory distress with or without fever affecting oxygenation as well as ventilation. One also needs to consider dengue shock syndrome due to increased prevalance in this part of world.

Emergency department management:
Includes quick history and rapid cardiopulmonary assessment' One needs to place pulse oximeter, begin oxygen therapy and consider

endotracheal intubation and initiation of mechanical ventilation if indicated by clinical deterioration (or arterial blood gases)

Portable chest x ray is done to confirm alveolar disease diffuse infiltrates/consolidation usually with normal sized heart.

Complete blood count, blood culture, coagulation profile, electrolytes urea creatinine, and liver functions are obtained.

Intravenous line is secured, if not successful, then introsseous access is obtained. Fluid bolus is administered if patient in shock as indicated by poor capillary refill.

Intravenous broad spectrum antibiotics are administered.

If hypotension and poor perfusion is seen despite fluid therapy consider dopamine at 10 microgram/kg/min and central venous pressure (cvp) monitoring may be initiated in the PICU.

One needs to initiate transfer land arrange transport to nearest pediatric intensive care unit by discussing with the pediatric intensivist.

PICU management is discussed elsewhere in detail.

(e) *Tension pneumothorax:* This is a medical emergency and should be promptly recognized and treated. Severe respiratory distress with shock due to decreased intrathoracic venous return caused by tamponade effect of air leak from lungs under tension compressing the heart resulting in acute fall in cardiac out put as indicated by hypoxemia, poor perfusion, and hypotension. Tension pneumothorax, if left untreated can result in cardiopulmonary arrest.

Clinically one finds absent or low breath sounds on the affected side as well as muffled heart sounds and shifted apical impulse. Chest X-ray shows mediastinal shift as well as compression with free air in the pleural cavity depressing the dome of diaphragm. Chest X-ray may take time immediate intervention may be indicated urgently. Chest needling on both side with 16 or 18 gauge iv cannula or scalp vein needle may be attempted to relieve tension pneumothorax.

However once chest x ray is obtained patient will require tube thoracostomy on the affected side in 2nd intercostal space anteriorly in mid clavicular line or alternatively in 4th intercostal space in mid axillary line(technique is discussed elsewhere)

Neuromuscular disorders leading to respiratory failure:

1. *Central hypoventilation syndrome:* Central hypoventilation may be congenital or acquired.

   Congenital form(Ondines curse)typically presents as cyanosis at birth readily responsive to mechanical ventilation (but not to oxygen therapy alone) with normal chest radiographs but repeated weaning failures. In less severe cases abnormalities in respirations during sleep such as periodic breathing, apnea or acute life threatening episodes may occur. This must be differentiated from reversible systemic processes such as sepsis, hypothermia, electrolyte abnormalities, hypocalcemia, hypoglycemia and seizures, CNS infections, intracranial hemorrhage, acute hydrocephalus. It also needs to be distinguished from obstructive sleep apnea due to hypertrophied tonsills, and adenoids, macroglossia (Down's syndrome), micrognathia (pierre robin syndrome, other oral or nasal congenital anomalies, temporomandibular ankylosis, vascular ring and vocal cord paralysis and post cleft palate surgical repair. Therapy is immediate ventilatory support if in acute respiratory failure. Doxapram, Theophylline, and Caffiene have been tried.Tracheostomy with home mechanical ventilatory assistance during sleep is commonly required. Recently noninvasive methods such as use of nasal mask continuous positive airway pressure (nasal CPAP) or non-invasive positive pressure ventilation (NIPPV) have been shown to be very effective and need for tracheostomy can be averted as well as progression of severe pulmonary hypertension can be slowed down.

2. *Guillain Barre syndrome:* (acute post infectious polyneuritis)

   This condition commonly presents as a post viral immune mediated paralysis affecting skeletal muscles as well as autonomic nervous system leading to profound muscle weekness ascending in nature with paresthesias. Diaphragmatic and intercostal muscle weakness leads to neuromuscular respiratory failure requiring mechanical ventilation in 20% of affected children. Therefore, frequent assessment of respiratory reserve is imperetive, such as forced vital capacity (fvc) falls below 15 to 20 ml/kg, maximum negative inspiratory pressure less than 20 to 30 cm H_2O, pCO_2 >50 mm of Hg.

Cranial nerve palsy and or cerebellar ataxia may be first presenting feature. More than 10% patients present with upper extremity weakness. Cerebrospinal fluid protein level is usually elevated > 45 mg/dl in absence of pleocytosis (cyto albuminoid dissociation) EMG shows lower motor neuron disease and nerve conduction velocity is delayed after 2-3 weeks following onset of disease. Rarely it can mimic brain death when patient gets unresponsive with non reactive pupils but normal EEG. Bladder and bowel dysfunction is common with hypertension due to effect on autonomic nervous system. Sinus tachycardia, bradycardia, ST and it abnormalities and postural hypotension.

Steroids have been empirically used.

Early plasmapheresis for removing autoimmune factors within 7 days of onset of disease has been found to be beneficial. Gamma globulin therapy has been demonstrated to be more effective when compared to plasmapheresis in a randomized trial.

However mainstay of treatment remains supportive.

Prognosis is usually good with recovery in three to four weeks however muscle power and neurological recovery may be incomplete and may be prolonged in few cases.

3. *Myesthenia Gravis:* Muscle weekness in Mysthenia gavis is attributed to immunological interference with neuromuscular transmission associated with acetyl choline receptor antibodies classical or juvenile myesthenia gravis can occur in children as young as two years however typically presents in adolescence in the congenital form onset of symptoms occurs within the first few days of life,and historically mothers do not have mysthenia gravis although a history of disorder in a sibling is common neonatal mysthenia gravis can be associated with severe generalized muscle weekness in two-thirds of patients,with history of mother suffering from myesthenia and maternal transmission of antibodies to acetyl choline receptor protein in the neuromuscular junction is believed to account for this disorder. Reason for acute respiratory failure in mysthenia are two fold: progressive muscle fatigue or excessive treatment with anticholinesterase therapy resulting in severe muscle weekness.

   Indications for intubation and mechanical ventilation include apnea,hypoventilation,or evidence of severe respiratory muscle fatigue.

   If muscle weekness is precipitated by viral infection or other systemic stress anticholinesterase agent administration may be life saving (myesthenic crisis) such as neostigmine or pyridostigmine. As a word of caution severe bronchospasm can occur as a side effect of anticholinesterase therapy. Myesthenic patients with muscle weekness due to cholinergic crisis usually show excessive parasympathetic activity such as salivation, lacrimation, diarrhea, bradycardia easily managed with atropine therapy. Muscle weakness improves on with holding anticholinesterase therapy.

   - Treatment:

     Prednisone therapy used as adjunct to anticholinesterase therapy in resistant cases as a treatment modality has been recommended.

     Thymectomy is useful in juvenile myasthenic cases and plasmapheresis performed before thymectomy has been found to be useful in resistant adult myasthenia gravis patients.

     Prognosis with anticholinesterase therapy with properly instituted supportive PICU management is good.

     Other cause of muscle weekness such as hypophosphatemia , hypermagnesemia, hypokalemia, aminoglycoside intoxication, must be avoided in these patients.

4. *Unilateral phrenic nerve paralysis:* This condition results from birth trauma to phrenic nerve and usually presents with respiratory distress in infancy. Fluoroscopy of the diaphragmatic motion is diagnostic. Diapragm moves upward with inspirarion. Usually adequate gas exchange can be maintained with CPAP alone or institution of mechanical ventilation, however, long term management will require surgical plication of

affected diaphragm. Other important causes of phrenic nerve injury include direct phrenic nerve injury during open heart surgery and aorto-pulmonary shunt procedures. 50% cases occur during closed heart surgery such as pulmonary artery banding, patent ductus arteriosus ligation. These patients are usually detected when patient fails to wean from the mechanical ventilation. Transcutaneous phrenic nerve stimulation can be applied in cervical region and if response is seen a plication surgery of diaphragm may be avoidable, specially in older child.

5. *Tetanus:* Tetanus is a rare condition however fatal if not managed properly. *Clostridium tetani* is anaerobic bacterium usually present in unhygenic humid surroundings important cause of neonatal tetanus. Tetanolysin and Tetanospasmin released at the neuromuscular junction cause severe muscle spasm leading to respiratory failure. In addition, laryngeal muscle spasm can induce acute asphyxia. Lock jaw/severe masseter spasm is common in 50 to 70% patients. Mental status is normal. Benzodiazepines, muscle relaxants and mechanical ventilation (3 to 5 weeks) are life saving in addition to antibiotics and proper attention to nutrition and PICU care. Currently mortality is down to 10 to 20% in good PICUs.
6. *Poliomyelitis:* Poliomyelitis represents an acute viral infection of the central nervous system that results in widespread muscle paralysis due to involvement of anterior horn cells and secondary respiratory failure.Usually there is minor febrile illness and/or gastroenteritis lasting one to two days. In less than a week later severe muscle pain, fever, irritability, paresthesias muscle fesciculations and diminished deep tendon reflexes in affected muscles ensue. In some cases it rapidly progresses to total paralysis.

   Cerebrospinal fluid shows mild pleocytosis with polymorphus in early course and mononuclear cells in later phase. Causative virus can be isolated from fecal and oropharyngeal specimens.Serological confirmation is made by identifying specific antibodies to polio virus.

   Bulbar palsy can result in loss of airway control due to pharyngeal muscle paralysis and can lead to airway obstruction and aspiration of pharyngeal secretions.

   Endotracheal intubation, mechanical ventilation chest physiotherapy remain the key treatment modalities.Tracheostomy is invariably required.PICU survival is good .Pediatric mortality can exceed 30% if good PICU facilities are unavailable. Chronic respiratory insufficiency can result from vocal cord paralysis, scoliosis, secondary respiratory restriction and central hypoventilation.

   Sporadic cases are still seen however the disease is close to be eradicated by universal immunization of pulse polio program.
7. *Spinal cord trauma:* High cervical injuries from 3rd to 5th cervical vertebrae result in loss of diaphragmatic,intercostal and abdominal muscle function.Accessory muscles in neck and shoulder remain intact.

   Endotracheal intubation and ventilation are invariably required.

   Lesions below C5 spare the diaphragm, however abdominal and intercostal function is lost resulting in paradoxical movement due to diaphragmatic contraction(chest retraction as diaphragm contracts during inspiration.)

   Acute respiratory failure, in a patient with spinal cord trauma is found more so due to following factors:

   Neurogenic pulmonary edema, chest wall and lung injury, as well as aspiration of gastric content in a comatose head injured patient. Neurogenic pulmonary edema tends to occur during spinal shock mostly thought due to excessive fluid resuscitation. As discussed earlier other accompanying chest and lung injuries contribute to severity of respiratory failure. Tracheostomy and long term mechanical ventilation is usually required. In patients with intact nerve conduction in phrenic nerve, radiofrequency electro phrenic pacing has been tried.

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CHAPTER 21

Pediatric Tracheostomy

Bala Ramachandran

The incidence of tracheostomies in children has decreased over the past several years.[1] This is due, in part, due to improved equipment and techniques of mechanical ventilation of infants and children. However, as survival rates for children with chronic medical conditions improve, more tracheostomies are being performed for non-airway indications in these patients.

HISTORY (FIG. 21.1)

Tracheostomy is a very old procedure. There are refe-rences to incisions into the windpipe in the Rig Veda, written between 2000 and 1000 BC.[2] Alexander the Great punctured the trachea of a soldier choking on a piece of bone with the tip of his sword in the 4th century BC.

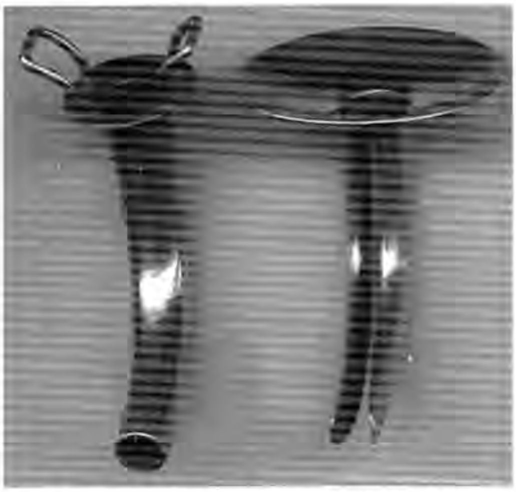

Fig. 21.1: Antique tracheostomy tubes made of silver (England, late 1800s) (Reproduced with permission from *www.tracheostomy.com)*

In the period between the 16th century and the early 1800s, tracheostomy was thought to be of no use. George Washington died in 1799 of acute airway obstruction. Tracheostomy was considered but vetoed by two of his three personal physicians.

In the mid 1800s, tracheostomy was advocated for the management of airway obstruction due to diphtheria. Chevalier Jackson, in the early 1900s, published his treatise on tracheobronchoscopy. Many of his techniques and equipment are used to this day.

The majority of tracheostomies were performed for inflammatory and infectious indications, mainly diphtheria. The advent of Sulfonamides and diphtheria immunization helped reduce the incidence of airway obstruction due to this disease. The poliomyelitis epidemic in the 1930s spurred new interest in tracheostomy. However, the availability of the Salk vaccine drastically reduced the incidence of paralytic polio. With improved endotracheal tubes and better care of the ventilated patient, the need for tracheostomies has continued to decrease.

Indications

Early in the history of tracheostomies, the procedure was usually performed for choking due to foreign body aspiration. Later on, 'croup' (a term used to refer to both laryngotracheobronchitis and diphtheria) became a common indication. It is only in the latter half of the 20th century that practices started changing toward the current indications. Today, fewer tracheostomies are performed for acute infections and a greater number are performed for more chronic medical conditions.[3] Carron *et al* showed that neurologial illness and prolonged ventilation formed the major proportion of pediatric tracheostomies, 28 and 26 percent respectively.[4]

There are three broad pathological categories of patients who will benefit from a tracheostomy.[5]

Airway Obstruction

Acute or chronic airway obstruction, when tracheal intubation is not possible or desirable. Examples include burns to the airway, trauma, subglottic stenosis and vocal cord paralysis.

Dead Space/Pulmonary Toilet

Tracheostomy will benefit patients with chronic medical disorders, such as chronic lung disease or broncho-pulmonary dysplasia, by reducing dead space and allowing easy access to the airway for clearing secretions.

Ventilation

Patients who require prolonged positive pressure ventilation will benefit from a tracheostomy. This includes patients with neuromuscular disorders, postcardiac surgery states and preterm neonates. A tracheostomy will prevent laryngotracheal damage caused by prolonged tracheal intubation (e.g. subglottic stenosis), allows easy access to the airway for suctioning, is less likely to be accidentally dislodged, will allow the patient to eat normally and is more comfortable. Some patients who are ventilator dependent may be able to come off the ventilator and breathe on their own after the tracheostomy.

The exact timing of a tracheostomy in children who require prolonged ventilation is a subject of considerable debate. It is common practice to perform a tracheostomy in adults who require tracheal intubation beyond two weeks. In children, especially with improved intensive care, an endotracheal tube can be safely left in place for several months. Arcand[6] has reported 19 tracheostomized patients who were intubated for an average duration of 29 days prior to tracheostomy. Of these, seven patients developed subglottic stenosis after mean intubation period of 40 days. Other important factors, which contribute to development of postintubation subglottic stenosis include: Movement of the tube,[7] number of times reintubation is required, trauma at the time of intubation, size and material of the tube, prematurity, presence of upper airway infection, and possible gastroesophageal reflux disease.[8]

The decision to perform a tracheostomy must be individualized for each patient, taking into consideration factors such as the age of the child, (neonates tolerate intubation longer than older children), the natural history of the disease process and the feasibility of discharge home with a tracheostomy.

TYPES OF TRACHEOSTOMY TUBES (FIGS 21.2 AND 21.3)

Tracheostomy tubes are available in various sizes, shapes and materials. The two basic shapes are an arc and an angled tube, which is a straight tube bent at 90°. Tubes may be made of silicone, polyvinyl chloride or metal. They may or may not have an inner cannula. Some tubes are fenestrated, that is, they have a hole at the cephalad end of the curvature that allows air to pass through the larynx. Tubes also come with and without cuffs. Neonatal tubes are shorter and have a short flange, whereas pediatric tubes of the

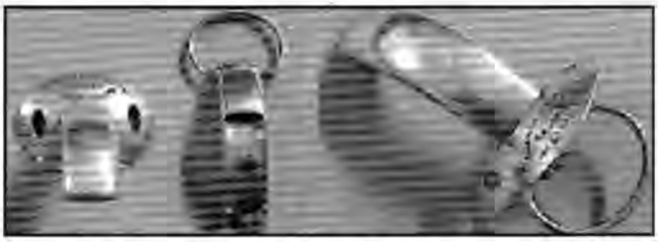

Fig. 21.2: Various pediatric and neonatal tracheostomy tubes (For color version see Plate 6)

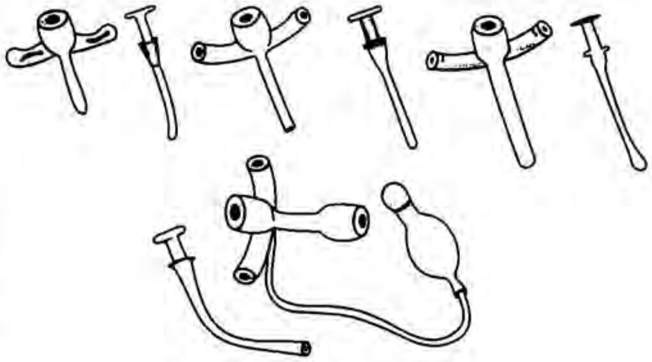

Fig. 21.3: Tracheostomy tubes

same inner diameter are longer and have a longer flange.

Specific Indications for a Tracheostomy[9]

See Table 21.1.

Tracheostomy Tubes Available in India

1. *Romsons* siliconized polyvinyl chloride (PVC) tracheo stomy tube with radiopaque line and soft flexible flanges for easy fixation on the neck. Available as Cuffed size 5-7 mm, Uncuffed size 4-7 mm.
2. *Portex:* Blue line portex tube (3.0-7.0 mm) has square ended flanges and a projecting collar. The tip is not beveled making it little difficult to insert through the vertical slit in trachea. 555 series specifically manufactured for pediatrics are not available in India.
3. *Shiley (Mallinkrodts)*
   - Standard Pediatric 3.0-5.0 mm.
   - Shorter neonatal 3.0-4.5 mm,
   - Longer pediatric 5-6.5 mm
   - Cuffed and uncuffed pediatric tubes are available.

CHOICE OF A TUBE

The correct choice depends on several factors, including the age, the reason for performing a tracheostomy and the expected duration of the tracheostomy.

In general, a tube of the same size or 0.5 mm larger than the correctly sized indwelling endotracheal tube will be adequate. A child who requires a tracheostomy to prevent chronic aspiration will need a tube that is relatively larger than someone who needs it for nocturnal ventilation. The tube should not be so large

Table 21.1: Specific indications for a tracheostomy

Cause	*Bypass airway obstruction*	*Assist pulmonary toilet assist ventilation*
Congenital	Subglottic stenosis Vascular ring Laryngeal web Vocal cord paralysis Tracheomalacia Pierre Robin Sequence	Postoperative after correction of congenital heart disease
Traumatic	Blunt injury to the neck, trachea or larynx Foreign body aspiration Severe facial injury damage to recurrent laryngeal nerve Inhalation burns to face, neck or upper airway	Prolonged coma following head injury
Infective	Retropharyngeal abscess Ludwig's Angina Deep neck infection with extensive cellulitis Tetanus	Meningitis Encephalitis, Poliomyelitis Pneumonia
Neoplastic	Laryngeal tumor Tracheal tumor Hemangioma Lymphangioma	Brain tumor Spinal cord tumor
Metabolic		Prolonged coma Cystic fibrosis Cardiac failure with ventilator dependence
Other	Prolonged tracheal intubation Head and neck surgery Obstructive sleep apnea	Neuromuscular disorders Myasthenia gravis Guillain-Barré syndrome

Adapted from Shott SR. Pediatric Tracheostomy. In: Myer CM, Ed. The Pediatric Airway. JB Lippincott; 1995;154.

as to damage the tracheal wall. The tube should extend at least 2 cm beyond the stoma but be no closer than 1-2 cm from the carina. In addition, the distal portion of the tube should be co-linear with the trachea to avoid complications.

Cuffed tubes are generally not used in children, except in special circumstances. If the pressure in the cuff is not adjusted carefully, it can contribute to damage to the tracheal epithelium. Metal tubes with an inner cannula are also not used commonly in children.

The tubes may be stiff at room temperature but generally become softer as they warm to body temperature. However, the standard polyvinyl chloride tube can stiffen with time, silicone tubes are much softer and may provide a better fit.

Fenestrated tubes help promote speech by allowing gas flow through the larynx, in addition to breathing through the stoma. A tube of a smaller diameter than the trachea will also provide the same benefit, if tolerated. Speech can be further enhanced by the use of a Passy-Muir 'speaking valve'. This is a one-way valve that allows air to enter during inspiration but blocks during exhalation, redirecting flow via the larynx, either through the fenestration or around the tube. However, some experts feel that fenestrated tubes promote the development of granulation tissue in the area near the fenestration.[ATS]

In selecting between tubes made by different manufacturers, it should be noted that the same number does not mean that the tubes are of similar dimensions. The specifications of the tube are clearly printed on the carton and in the product literature and should be carefully studied. Generally, the variety of ready-made tubes will accommodate most patients. Occasionally there may be a patient whose needs cannot be met by a ready-made tube. Some physicians have modified existing tubes but this practice should be discouraged since it is difficult to eliminate sharp edges and the structural integrity of the tube will be affected. Most companies will manufacture a custom made tube to suit an individual patient, but this, obviously, takes time.

TECHNIQUE

Surgical details are beyond the scope of this discussion.

In infants and small children, it is harder to identify the airway because of anatomical differences such as the small size, the short chubby neck and the higher position of the larynx. In addition, pediatric patients may not cooperate adequately with local anesthesia alone. Therefore, tracheostomy is usually performed under general anesthesia in the operation theater (OT). Only in acute emergencies or when the patient is too unstable to be transported to the OT, tracheostomy is performed at the bedside. Since the pediatric trachea can be difficult to differentiate from the surrounding tissues, tracheostomy is often performed over a bronchoscope or endotracheal tube. The surgeon will usually place a retraction suture on either side of the tracheal incision. The tracheostomy ties are also secured tightly. A properly fastened tie will allow one adult finger to be inserted beneath it. Post-operatively, these sutures are labeled clearly "Right" and "Left", and taped to the patient's chest. All personnel, taking care of the patient, should be familiar with these sutures. In the event of accidental decannulation before the tracheostomy tract has matured, it can be extremely difficult to identify the opening in the trachea. Under these circumstances, the stay sutures can be gently pulled to either side and this will generally make the tracheal opening visible, allowing a new tube to be inserted.

Percutaneous Technique (PT)[5]

Under pressures of economic efficiency and patient safety, there have been a growing number of publications on percutaneous tracheostomy (PT). As we have not found a formal definition of PT elsewhere, we shall refer to it as the insertion of a tracheostomy tube without direct visualisation of the trachea, using minimal dissection, through the smallest incision possible.

Percutaneous tracheostomy is also an ancient practice. In the 16th century, Santorio described the placement of a pointed tube through the skin into the trachea (Sercer, 1962). Mortality with this stab technique must have been quite high, and Jackson condemned its use: '....it is small wonder if the percentage of mortality is almost as high as of stab wounds, inflicted with homicidal intent' (Jackson, 1909). But the needs of methods for emergent and military use prompted continued research. Sheldon *et al* (1957) reported the use of a cutting instrument passed into the trachea along a guide needle, over which a tracheostomy tube was introduced. They stated that this required less than a minute and had minimal bleeding, no morbidity, and no mortality in 4 years use. It was not stated how many procedures were performed, and there is little further mention of their technique in the literature. In 1969, Toye and Weinstein reported the first dilatational technique of PT. This involved inserting a tracheostomy tube loaded over a curved dilator. They required only 30 seconds to perform the task, and in 1986 reported 94 cases, with no surgical mortality (Toye, 1986). In 1985, Ciaglia *et al* reported the use of a percutaneous nephrostomy set for tracheostomy using the Seldinger technique (Seldinger, 1953) to pass dilators over a wire into the tracheal lumen. The initial 26 patients suffered no complications.

Technique of Insertion of Percutaneous Tracheostomy

The technique used now is based on the principles previously described by Ciaglia *et al* (1985). A split sheet draping system is used to facilitate better coordination between the anesthesiologist and the surgeon. In order to avoid puncture of the tube, the endotracheal tube is withdrawn immediately below the vocal cords. This also helps avoid dilating the trachea alongside the endotracheal tube.

The skin incision is made to accommodate the largest tracheal dilator. The trachea is then punctured between either the first and second or the second and third tracheal rings with a 16-gauge catheter. The needle is removed and a guidewire is passed through the catheter. If it does not pass easily, this may be the result of retrograde passage of the guidewire, and tracheal puncture is repeated. A hemostat (artery forceps) is used to spread the investing fascia of the neck along the path of the guidewire to facilitate tracheal dilatation. This may be done prior to tracheal puncture to facilitate palpation of the cricoid cartilage and the tracheal rings.

Serial dilators are passed over a Teflon guiding catheter, which has been passed over the intratracheal guidewire. A tracheostomy tube is then placed over the appropriate size dilator and both are advanced into the trachea.

The endotracheal tube is removed after confirming proper placement of tracheostomy tube by demonstrating carbon dioxide return. This avoids the potential problem of hypoventilation related to preferential air passage out of the endotracheal tube. The tracheostomy tube is then secured. No sutures are required around the skin incision as it fits comfortably around the tube. A tight fit is to be avoided since it predisposes to surgical emphysema. The tube may be held in place by suturing the flanges to the neck skin. A tape is then tied from one side of the flange to the other round the back of the neck. One end of the tape is knotted to one side of the flange while the other is passed through a tubing of suitable length. This protects the skin from the rubbing of the tape. The free end of the tape is then knotted to the other end of the flange and is adjusted so that the tube is held freely, but not tightly, in place. All manipulations are done keeping the neck in slight flexion. If they are done with the neck extended, the tube will loosen on subsequent flexion and accidental decannulation will occur.

POSTOPERATIVE CARE

A chest X-ray is obtained immediately after the procedure to look at the position of the tip of the tracheostomy tube. This is to ensure that the tip does not impinge on the carina. The X-ray will also show the presence of surgical emphysema. It is best to keep the patient in the PICU postoperatively since it may not be possible to provide the degree of nursing care required elsewhere to monitor the patient closely and detect accidental decannulation immediately.

The patient should receive humidified oxygen or air to prevent tube obstruction and airway irritation by dried secretions. The wound site should be cleaned at least twice a shift with half strength hydrogen peroxide and sterile gauze.[1] This is to keep the area clean, promote healing and prevent infection. The tracheostomy tube should be suctioned at regular intervals with a suction catheter that passes freely but is large enough to clear secretions effectively. The tip of the catheter should not be allowed to extend beyond the end of the tracheostomy tube to prevent damage to the tracheal epithelium. If the tracheostomy tube has an inner cannula, this should be cleaned regularly (at least every eight hours) with soap or hydrogen peroxide and rinsed in sterile water before being replaced. Disposable inner cannulae can also be used. The tracheostomy ties are usually changed on the third day after surgery and then daily. The tracheostomy tube is generally changed by the surgeon on the fifth post-operative day, though some people have stated that they can safely be changed as early as the third post-operative day.[10] Unless the patient is already in the PICU, this should be done in an area where immediate control of the airway can be accomplished, should there be any problems. Once the tube has been changed, it is safe to transfer the patient to a ward where the staff are experienced in the care of patients with tracheostomies.

Looking after tracheostomies in an infant presents special challenges. The infant's neck is short and often the patient has poor head control. Under these circumstances, the tracheostomy opening can easily be occluded by the patient's chin or roll of fat when the neck is flexed. Adapters, such as a tracheostomy tube guard, heat-moisture exchanger or another device may be required to prevent such occlusion.

The following equipment should always be available wherever a patient with a tracheostomy tube is cared for: suction catheters of the correct size, working suction, appropriately sized bag and mask, humidified oxygen, a fresh tracheostomy tube of the same size and one size smaller, tracheostomy ties and scissors.

ROUTINE CARE

There is considerable variation between physicians and centers regarding routine tracheostomy tube care practices. There is also a lack of good evidence to support one practice over another and therefore choices are usually left to individual preferences.

Tube Change

The tracheostomy tube must be changed regularly to prevent accumulated secretions from obstructing the lumen and minimize the risk of infection. Tubes are changed most often once a week, but the frequency ranges from daily to monthly.[11] At the time of tube change, the stoma must be examined for evidence of breakdown, irritation or infection. A water-based lubricant will assist reinsertion of the tube. The individual tube may be cleaned, disinfected and reused in order to reduce expenditure. Polyvinyl chloride tubes (Shiley or Portex) become stiff with time and should not be reused once they have lost their flexibility. However, this usually does not occur until after 3-4 months. In addition, if several tubes are rotated, an individual tube may be used for as long as 6 months to a year before being discarded. Silicone tubes do not stiffen but should be inspected periodically for cracks or tears. In between uses, a tube should be cleaned thoroughly with half-strength hydrogen peroxide or half-strength household vinegar or clean water and a mild detergent. Pipe cleaners can be used to clean the interior, if available. The tube should be rinsed with sterile saline after cleaning and then air-dried before being reused.[11] Companies that manufacture tracheostomy tubes do not recommend using commercial disinfecting solutions to clean tubes since the solution may react with the material and degrade it.

Routine Cuff Deflation

In some centers, tracheostomy cuffs are deflated on a regular schedule in order to minimize damage to the tracheal mucosa by the inflated cuff. However, no evidence exists to show that this technique is beneficial.

Tracheostomy Ties

Three different types of tracheostomy ties are available: twill tape (the commonest), special Velcro® ties and beaded metal chains. Twill tape is used most often and should be changed whenever it becomes wet or is soiled. If the tie is being changed by a single person, the new tie should be inserted before the old one is cut. The tape should be tied securely with a triple knot on the side of the neck to prevent accidental decannulation. A properly secured tie will allow only one adult finger to be inserted underneath it when the neck is flexed forward. The tie itself may cause irritation and skin breakdown. This can be alleviated by placing foam pads between the tie and the skin. In addition, care should be taken to ensure that hair is not caught beneath the tie. In order to minimize skin damage, the side of the knot can be alternated.

Velcro ties are easier to use but more expensive. Beaded stainless steel chains are also effective and maintain constant tension. They do not trap moisture and cause less irritation than cloth ties.

Suctioning

The frequency of suction is dependent on the amount and quality of secretions, the age of the patient and the ability to generate an effective cough. Initially, tubes are generally suctioned whenever required to clear secretions and every two hours. Later on, the frequency is tapered to as needed basis. If a patient with a mature tracheostomy does not have secretions that require suction, the tube should still be suctioned in the morning and at bedtime to assess patency.

The largest suction catheter that will pass freely through the tracheostomy tube should be used,[12] since this will clear secretions most efficiently. The tip of the suction catheter should be inserted just beyond the end of the tracheostomy tube. A premeasured technique should be used wherein the depth of insertion is determined prior to insertion of the catheter by looking at a tracheostomy tube the same size as the patient's. A suction catheter with length graduations will facilitate insertion to the correct depth. Deep suctioning, in which the catheter is inserted until resistance is felt, should not be used routinely since this will lead to damage to the tracheal epithelium. Suction should be applied both during insertion and withdrawal of the catheter and the catheter should be twirled between the thumb and forefinger (rather than rotating the entire hand). The duration of suctioning should not exceed five seconds.

It is routinely suggested that instillation of normal saline before suctioning may help liquefy thick secretions. However, studies do not support this notion and the instillation of saline may cause desaturation and contamination of the lower airway with unsterile fluid. Therefore, the routine instillation of saline is not recommended.

Clean Versus Sterile Technique for Suction

Typically, a "Sterile Technique" is used in hospital, that is, sterile catheter and sterile gloves. However, it is sufficient to use a "Clean Technique" when the patient is at home (clean catheter, non-sterile disposable gloves or freshly washed clean hands).

Since secretions pass through the catheter in onl one direction, it is more important to have a clea external surface than a sterile interior. A clea catheter is used with freshly washed hands or clea unsterile gloves. If hands cannot be washed wit soap and water, an alcohol or chlorhexidine base disinfectant hand rub may be substituted. Afte suctioning, the catheter is flushed with tap water t remove secretions, the outside of the catheter wipe with alcohol and the catheter air dried and store in a clean, dry place. The interior may be flushe with hydrogen peroxide to remove tenaciou secretions. The catheter may be reused as long as i is intact and transparent enough to inspect th interior. The catheter can also be soaked in commercial disinfectant solution, if desired, but ther is no evidence to suggest that one technique i superior to another.

Stoma Care

The tracheostomy stoma should be kept clean an dry. The stoma can be cleaned with soap and water taking care that liquid does not enter the trachea Moisture and irritation will promote the formatio of stomal granulomas, which may require fulguration with Silver Nitrate. Some parents apply a crea of clotrimazole and 1 percent hydrocortisone to hel minimize irritation.

Humidification

A tracheostomy bypasses the normal mechanisms o filtration, heating and humidification. Cold unhumidified gas irritates the airways, cause secretions to thicken, damages the airway epitheliu and can eventually cause deterioration of pulmonar function and increased risk of infection. Therefore the gas breathed through a tracheostomy must b heated and humidified. However, factors such as th ambient temperature, the use of air conditioning an the relative humidity should also be considered an the ideal goals must be balanced against the issues o cost effectiveness and convenience.

The most efficient method of humidification is th use of a heated bubble-through humidifier. Thi technique is also expensive and cumbersome. A larg volume jet nebulizer may be used. The easies method of humidification is to use an "artificial nose or a "Heat Moisture Exchanger". These come with and without filters and another type, known as a hygroscopic condenser humidifier is also available. All of these are attached to the tracheostomy tube, trap moisture when the patient exhales and release it to the inhaled gas. They are efficient, convenient, relatively inexpensive and are ideal for mobile patients. However, they add extra dead space to the system and thick secretions can easily obstruct them. They also cannot be used with speaking valves since patients using a speaking valve exhale through the larynx. They should not be left in place at night since obstruction by secretions may go unnoticed while the user is asleep.

Speech and Swallowing Assessment

All patients with a tracheostomy should be referred for speech therapy. The speech therapist will assess the patient and provide the necessary equipment and techniques to promote speech development. Normal speech via the patient's larynx is the desirable goal. For this to be possible, the tracheostomy tube diameter should not exceed two-thirds of the tracheal lumen, or the tube should be a fenestrated one.[ATS] This will allow enough air to pass through the larynx to allow vocalization. A one-way Passy-Muir speaking valve can also be used if the patient is stable, does not have thick secretions and can tolerate it. In those patients who cannot speak through the larynx, alternative methods of communication are available, including sign language, signboards, or an electrical larynx.

Evaluation of swallowing is an integral part of the speech therapy consultation. The presence or absence of aspiration of solids and liquids can be determined by adding methylene blue or blue food color to the swallowed items. Any blue colored tracheal secretions over the next few hours indicates aspiration. If there is any doubt, a formal video fluoroscopy should be performed. This should be done with the cuff inflated and deflated, with and without a speaking valve, if the patient is using these devices. In Indian setting role of speech therapist may be taken by the primary pediatrician along with mother being taught care of tracheostomy and speech promotion.

PARENT TEACHING AND HOME CARE

It was commonplace in the early parts of the 20th century to permanently keep all children with tracheostomies in a special "tracheostomy ward" in hospital. However, nowadays, the goal is to send the patient home since this is the best environment for the child. Preparing the home and family to properly look after a child with a tracheostomy is a daunting task. Discharge planning is a multidisciplinary process that should begin even before the tracheostomy is performed. The most important factor is the availability of committed family members who will accept responsibility for the child and can be adequately trained.

At least two responsible adults should be trained in all aspects of tracheostomy care. This should include changing the tracheostomy ties, suctioning, stoma care, changing the tracheostomy tube, cleaning the equipment and recognizing emergencies. They should practice all these procedures and become comfortable with them while the child is still in hospital. Cardiopulmonary resuscitation should also be taught. A Tracheostomy Care Manual should be provided, if the hospital does not have one, ready-made manuals are available either free or for purchase through the Internet.[12-14]

The supplies required for home care include a suction machine, portable suction (for use when the patient is out of the house), replacement tracheostomy tubes of the same size and one size smaller, tracheostomy ties, suction catheters, oxygen supply, ventilator and related equipment (if the patient is ventilated), ambu bag, and humidification equipment. All the equipment for home use should be used before discharge in the hospital to confirm that they work and to identify problems. In Indian set-up usually mother and a home nurse can be trained to maintain and trouble shoot the care of a tracheostomized child. Primary care pediatrician or pulmonologist should be available by phone round the clock for these families, with regular outpatient follow-up, and if necessary to evaluate the patient in emergency room at the hospital.

Monitoring

Home monitors are often used for patients with tracheostomies. However, no monitor is infallible and false alarms are a problem with many. More importantly, the presence of a monitor may give a false sense of security to both the physician and the family. The best monitor is a well-trained, attentive caregiver. Various factors, including the stability of the patient and cost, should be considered when deciding whether to prescribe a monitor.

Attempts should be made to make the child's life as normal as possible. Children with tracheostomies are at risk for developmental delay in speech, language, motor, feeding and social skills.[15] Depending on the individual circumstances, it may be possible for the child to attend regular school. Normal play activities can be permitted, with the exception of contact sports and water sports (including swimming).

Regular follow-up is essential. This may include visits by a pediatrician home nurse, or visits to the clinic as convenient. In addition, the patient's airway should be evaluated every six to twelve months by flexible or rigid bronchoscopy in order to assess the airway and detect complications.

DECANNULATION

Decannulation is performed when (1) the original need for the tracheostomy is no longer present and (2) the patient is able to maintain a safe and adequate airway independent of the tracheostomy tube.[11]

Decannulation may be performed by sequential downsizing or in a single-stage procedure. In either case, the airway must be examined by formal endoscopy to check the anatomy, functional patency and for any granulations. The sequential downsizing technique is the traditional technique. The tracheostomy tube is progressively downsized over a period of days to several weeks. When the patient is able to tolerate the smallest tube, it is removed and the stoma covered by a dressing, so that the child is forced to breathe through the larynx and nose. This technique is advantageous in that it can be performed as an outpatient basis initially and the child gets progressively accustomed to breathing through the upper airway. However, the procedure may be difficult in small children, since downsizing the tube size in an already small airway will increase the airway resistance tremendously and increase the chances of mucus plugging. In the one-step procedure, the airway is evaluated endoscopically and if it is thought to be adequate, both anatomically and functionally, the tracheostomy tube is removed. Either technique is acceptable and the choice is usually dependent on the individual preferences of the physician. In both cases, the patient should be observed in the hospital for at least 2 days to ensure that he can maintain the airway properly without assistance.

When the patient is decannulated, the airway dead space doubles and resistance increases 300 per cent. These factors can lead to 'decannulation panic' in the patient.[4] In such instances, progressive downsizing may be a better choice rather than a one-stage procedure.

Occasionally, the tracheostomy stoma may not close and will have to be closed surgically.

COMPLICATIONS

It is estimated that between 20 and 50 percent of pediatric patients with tracheostomies will have complications.[11] Younger children have more complications than older ones and emergency tracheostomies have more complications than elective ones.

Complications can be divided into early (occurring with one week of the procedure) and late (occurring after one week). Early complications have been reduced to less than 0.5 percent due to improved techniques of anesthesia, surgery and post-operative intensive care. There is a direct relationship between the length of the tracheostomy and the incidence of late complications (11% with tracheostomy < 100 days, 55% for 100-500 days and 80% > 500 days).[11]

Early Complications

1. Obstruction usually by blood clot or secretions or false passage.
2. *Hemorrhage:* This is the most common early complication. The tracheostomy cannula can irritate the airway and cause coughing, which results in bleeding. Meticulous surgical technique and correct selection of the tracheostomy tube will help minimize this problem. Mild bleeding can be controlled with loose packing with a topical hemostatic agent (Gelfoam or Surgical). More severe bleeding may indicate damage to a major

blood vessel and may require exploration in operation theater and surgical control.

3. Subcutaneous emphysema.
4. Pneumothorax or pneumo-mediastinum.
5. Esophageal injury.
6. Recurrent Laryngeal Nerve damage.
7. Tracheitis and infections around the stoma.
8. *Accidental decannulation:* The risk of accidental decannulation is highest in the first few days after surgery and of serious potential for mortality and morbidity. It may be difficult to re-insert the tracheostomy tube before the tract has healed and using force may result in the creation of a false passage. All medical and nursing staff that take care of the child after a tracheostomy, must be trained to recognize and handle this problem. Equipment, including tracheostomy tubes of the same size and one size smaller and airway emergency equipment must be kept in readiness at the bedside.In case tracheostomy can not be inserted, bag mask ventilation should be performed with occlusion of tracheal wound/or an endotracheal tube should be placed via oral route untill ear, nose, throat specialist (ENT) or the intensivist can try placing the tracheostomy with the help of a laryngo bronchoscope.

Late Complications

1. *Tracheal wall erosion:* This problem can be minimized by adequate humidification and good tracheostomy care so that drying, infection mucosal irritation and ulceration are avoided. If erosion occurs into the innominate artery, catastrophic hemorrhage can occur. Any bleeding from the tracheostomy must be evaluated. Bleeding from suctioning must be differentiated from sentinel bleeding due to arterial wall erosion. If the erosion occurs into the esophagus, a tracheo-esophageal fistula will result.[16]
2. *Tracheal granulomas* These frequently occur above the tracheal stoma. Small granulomas can be watched but larger or pedunculated ones must be removed surgically, or by endoscopic laser.
3. Subglottic and tracheal stenosis
4. Tracheomalacia
5. *Suprastomal collapse:* Severe suprastomal collaps may make decannulation impossible and requir reconstruction:
   a. Persistent tracheocutaneous fistula
   b. Recurrent tracheitis and bronchitis

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CHAPTER

22

Acute Severe Asthma Management in Pediatric Intensive Care Unit

Praveen Khilnani

Asthma has been defined as recurrent reversible lower airway obstruction with air trapping due to inflammation, mucosal edema and bronchospasm mediated by inflammatory mediators such as eicosanoids, leukotriens, platelet aggregating factors.

T lymphocytes release cytokines that recruit eosinophils and mast cells in airway. Direct allergens and indirect stimuli result in mast cell degranulation releasing histamine, leukotriens, prostaglandins, and cytokines leading to stimulation of macrophages, eosinophils and neutrophils resulting in more inflammation. Inflammatory mediators cause degradation of NO (nitric oxide), enhance cholinergic transmission, decrease cAMP, resulting in bronchoconstriction, mucosal edema and mucus production causing further airway obstruction. Endothelin 1 (growth factor) stimulation results in smooth muscle hyperplasia, and epithelial shedding causes airway hyper-responsiveness.

Clinical Features

History of nasal allergies, eczema, food allergies and a family history of asthma is important consideration in history. Hallmark of clinical examination is respiratory distress with wheezing triggered by viral upper respiratory infection, exposure to cold, exercise induced, or unknown allergens. Worsening respiratory distress causes tachypnea, tachycardia, sweating, anxiety, nasal flaring, suprasternal retractions and intercostal retractions. This may progress to silent chest, lethargy, cyanosis, bradycardia and respiratory arrest.

Asthma Management (Flow chart 22.1)

Mainstay of Treatment for Asthma remains Beta agonists and glucocorticoids (bronchodilatation and antiinflammatory action).

It is now clear that metered-dose inhalers (spray) in combination with spacer devices are as efficacious, if not more, as nebulizers[1] even in acute severe asthma.[2,3] They should thus be proposed as first line therapy. Since the dose which reaches the lower airways can be fairly low and also highly variable, (1 to 13% of the delivered dose) it is important to increase the number of puffs. Consequently, it would be more adequate to administer higher doses using puffs every 30 to 60 seconds than several puffs simultaneously.

Breathing through a mouthpiece improves lung, deposition, but in general this is only possible after the age of 3 years. The use of spacers in severe asthma implies that the patient has to be compliant, can master the breathing technique. Cost-effectiveness and simplicity of use are the main advantages of the technique.

Dry powder inhalers can be used in acute asthma if the inspiratory flow is greater than 30 L/min. This is generally the case in asthmatic children more than six years of age even during an acute crisis. Bronchodilators rapidly relax the airway smooth muscle cells, thus reversing the bronchospasm, until the anti-inflammatory effect of steroids is attained. Care should be taken to obtain early and maximal bronchodilation with minimal systemic adverse effects. As mentioned earlier, Inhaled β-2-agonists are the usual first line treatment, in association with anticholinergic agents in severe cases. The use of theophylline is rarely recommended nowadays. Nebulized β-2 agonists, via a mouth piece (3 yrs and older) or a facial mask (less than 3 yrs), are the most commonly prescribed first line therapy. Dry powder inhalers with a spacer device can be used in young children. This method is fairly straightforward since it does not require the active participation of the patient.

In pediatric age group, it is important to use nebulizers whose function remains identical even if the device is not held vertically. It is preferable to use oxygen rather than compressed air in order to decrease desaturation caused by ventilation-perfusion mismatch, with a flow rate of 6 to 8 L/min to ensure proper granulometry of the nebulized substance. Bronchodilatation is generally obtained after 10 to 15 minutes, and will last 3 to 4 hours. The optimal nebulized dose is still a controversial issue, but most practitioners repeat nebulization every 20 to 30 minutes within the first hour.

The side effects of β-2 agonists include tachycardia, distal tremors, agitation, paradoxical bronchospasm, hyperglycemia and hypokalemia. In one study, nebulized salbutamol (125 μg/kg) induced hypokalemia was correlated to the decrease in the respiratory rate and the increase in peak expiratory flow rate. Paradoxical deterioration of respiratory function (increased airway resistance and desaturation) during β-2 agonists administration is more prevalent during infancy. It is due to ventilation-perfusion mismatch, selective hyperosmolarity of the nebulized solution over time or rapid modifications of the compliance of the airways which become more collapsible.

Continuous Nebulization

Continuous nebulization is recommended in more severe cases in which the risk of inadequate bronchodilatation overwhelms the risk of catecholaminergic toxicity. The diluted bronchodilator is placed into a large syringe which is mounted onto an electric pump in order to deliver a continuous flow of the drug into the nebulizer for aerosol delivery system. Initial recommended flow rate is 20 ml/hr. That will be subsequently adjusted in order to maintain a constant volume of 2 ml in the nebulizer. Continuous nebulizations are generally well tolerated clinically Transient elevations of CPK-MB and minor asymptomatic electrocardiographic changes can be observed Typically salbutamol at 5 mg/HR to 15 mg/HR may be used with monitoring of heart-rate.

The theoretical advantage of epinephrine over other sympathomimetic agents lies in its added "alpha effects" mucosal vasoconstriction may reduce edema. However, inhaled epinephrine does not appear to be more efficacious than beta-2 agonists.[4] In 90 children with acute asthma, subcutaneous epinephrine was superior to terbutaline nebulization (in particular when FEV1 was < 60%), although less well tolerated.[5] Parenteral epinephrine should be used only in life-threatening acute attacks, or in the presence of serious systemic allergy with anaphylactic shock.

The most commonly used inhaled anticholinergic agent is ipratropium bromide. Beta-2 agonists and anticholinergic agents have synergistic effects, in particular in severe asthma (FEV1 < 30%).[6,7] They are indicated if treatment with beta-2 agonists fails or is poorly tolerated. Anticholinergics should not be administered in moderate asthma, and are not usually administered alone.

In acute exacerbations, the use of long acting β-2 agonists such as formoterol and salmeterol cannot be recommended for acute asthma management Moreover, regular treatment with inhaled salmeterol modifies the dose-response curve to the inhaled short-acting β-2 agonists, which may be less efficacious in such patients Fuglsang.[8]

Corticosteroids

Steroids reduce the inflammatory component of bronchial obstruction, decrease mucus production and mediator release, as well as the late phase (cellular) inflammatory process. Noteworthy is their capacity to rapidly (within one hour) reverse the tachyphylaxis induced by β-2 receptor desensitization which occurs after prolonged β-2 agonist use. Overall they have a dual action: the early facilitation of β-2 agonist bronchodilatation followed by a later anti-inflammatory role. This explains why they should be administered very early.

The golden rule in acute asthma is to administer steroids via the systemic route.[9] The parenteral route does not offer any advantages over the oral route unless the child has GI disturbances. In very severe cases, the parenteral route is widely used. The optimal dose of steroids in acute asthma in children vary widely (1 to 50 fold),[10] but it is wise to keep treatment duration to a minimum in order to limit adverse effects on growth. The maximal effect is obtained 6 to 12 hours after administration of the drug. No tapering is required if it is administered for less than 15 days.[11] Systemic steroids are relatively contraindicated if the patient has been exposed to varicella-zoster virus during the preceding month.

Inhaled Steroids

High dose inhaled steroids have been shown to rapidly improve pulmonary function in acute asthma in adults and children. This could be due to the vasoconstricting effects of the drug. In acute exacerbations, a short course of high systemic steroids is much more reliable and less expensive than high doses of inhaled steroids which should be reserved for selected cases where there is a special reason to avoid the use of systemic steroids. Preventive inhaled steroids should be discontinued during an acute episode, and resumed after the acute episode either at a higher dose or in addition with other therapies such as inhaled long-acting β-2 agonists, antileu-kotrienes or theophylline.

Intravenous Agents

Subcutaneous or intravenous bronchodilators are not recommended as first line therapy in children, unless the inhaled route cannot be used.

Parenteral β-2 Agonists

The use of parenteral beta-2 agonists is limited by the high incidence of systemic side effects. However, the pharmacological profile of the drug is more predictable when administered via the intravenous route, compared to the inhaled route. Systemic beta-2 agonists are indicated in severe cases, when continuous nebulizations are ineffective.

Addition of 15 µg/kg of intravenous salbutamol in the early treatment of children with acute asthma curtailed the clinical progression of asthma. The differences in side-effects were not statistically or clinically significant (except higher proportion of tremor at two hours in the intravenous salbutamol group compared with the control group).

Subcutaneous self injections of bronchodilators may be of use in children with brittle asthma (patients prone to very abrupt attacks).

Theophylline

Despite all its theoretical advantages,[12] intravenous theophylline has not quite maintained its place in the acute asthma therapeutic arsenal. This is due to its toxicity, and the plasma level monitoring requirements. Moreover, its association with a beta-2 agonists has not been shown to improve efficacy.[13]

Other Therapies

Magnesium: Intravenous magnesium have been tried but rarely avert admission from the (50 mg/kg/dose IV). From the emergency room to the PICU. Using intravenous ketamine requires admission to the PICU.

Admission to the PICU

Proper outpatient management, compliance and followup of an asthmatic child, can prevent severe exacerbations minimizing the need for hospitalization. Aggressive, in hospital, management of asthma can usually prevent Pediatric intensive care unit (PICU) admission, however an unknown percentage of children will go on to require PICU admission.

A small percentage of PICU patients unresponsive to coventional management (oxygen, subcutaneous epinephrine, continuous inhaled bronchodilators, and steroids) will require mechanical ventilation.

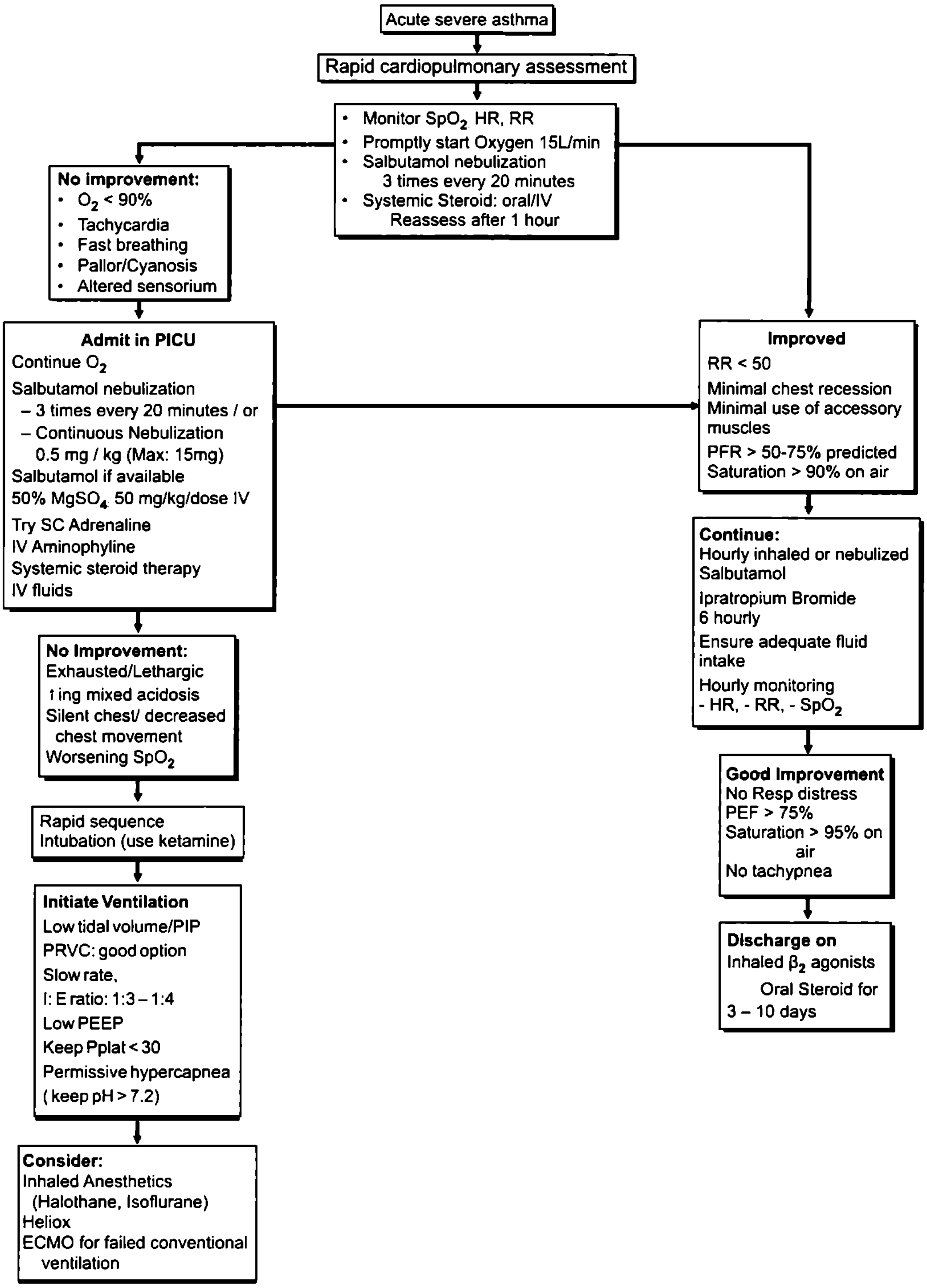
Mechanical ventilation of a struggling asthmatic child is a challenging task, not to be taken lightly, due to associated risk of airleak, or cardiovascular collapse due to tamponade effect of hyperinflation.

Following is a discussion of indications of mechanical ventilation, initiation of ventilation, ventilation strategies, sedation and respiratory care during mechanical ventilation of a critical child with acute severe asthma.

Indications of Intubation and Mechanical Ventilation

The arterial blood gas is not always a good indicator of the need for mechanical ventilation. The PaO_2 may fall early in asthma crisis because of a maldistribution of Ventilation and Alveolar Perfusion

Flow chart 22.1: Treatment of acute severe asthma in PICU


Acute severe asthma
Rapid cardiopulmonary assessment
• Monitor SpO2 HR, RR
• Promptly start Oxygen 15L/min
• Salbutamol nebulization 3 times every 20 minutes
• Systemic Steroid: oral/IV Reassess after 1 hour
No improvement:
• O2 < 90%
• Tachycardia
• Fast breathing
• Pallor/Cyanosis
• Altered sensorium
Admit in PICU
Continue O2
Salbutamol nebulization
– 3 times every 20 minutes / or
– Continuous Nebulization 0.5 mg / kg (Max: 15mg)
Salbutamol if available
50% MgSO4 50 mg/kg/dose IV
Try SC Adrenaline
IV Aminophyline
Systemic steroid therapy
IV fluids
No Improvement:
Exhausted/Lethargic
↑ing mixed acidosis
Silent chest/ decreased chest movement
Worsening SpO2
Rapid sequence Intubation (use ketamine)
Initiate Ventilation
Low tidal volume/PIP
PRVC: good option
Slow rate,
I: E ratio: 1:3 – 1:4
Low PEEP
Keep Pplat < 30
Permissive hypercapnea (keep pH > 7.2)
Consider:
Inhaled Anesthetics (Halothane, Isoflurane)
Heliox
ECMO for failed conventional ventilation
Improved
RR < 50
Minimal chest recession
Minimal use of accessory muscles
PFR > 50-75% predicted
Saturation > 90% on air
Continue:
Hourly inhaled or nebulized Salbutamol
Ipratropium Bromide 6 hourly
Ensure adequate fluid intake
Hourly monitoring
- HR, - RR, - SpO2
Good Improvement
No Resp distress
PEF > 75%
Saturation > 95% on air
No tachypnea
Discharge on
Inhaled β2 agonists
Oral Steroid for 3 – 10 days

(VQ mismatch). However, this mismatching is not all that important, and an $FiO_2 > 0.60$ is rarely needed to obtain $SpO_2 > 90\%$. In the initial phase of asthma crisis, the $PaCO_2$ is < 40 mm Hg. As status asthmaticus progresses and the child becomes exhausted, $PaCO_2$ rises.[14] $PaCO_2$ reflects the severity of bronchospasm.

Arterial blood gas criteria are indicative of the need for close monitoring. Mechanical ventilation may be initiated when blood gas parameters worsen or there is deterioration in clinical condition:

$PaO_2 < 60$ mm Hg or cyanosis is not corrected by oxygen administration $PaCO_2 > 40$ mm Hg and rising more than 5 mmHg/hour, and worsening metabolic acidosis.

The decision to intubate and ventilate a child with status asthmaticus is commonly based on clinical criteria:[15]

- Respiratory muscle fatigue, obvious exhaustion,
- Diminution of chest expansion during respiratory movements,
- Diminution of air entry in the lungs: quiet chest, absence of audible wheezing, pulsus paradoxus > 20-40 mmHg (inspiratory decline in systolic blood pressure), deterioration of mental status (lethargy, agitation, confusion, coma) and diaphoresis in recumbent position,
- Several signs are generally present together when mechanical ventilation is indicated. Respiratory arrest, gasping or cardio-respiratory arrest are, of course, absolute indications for mechanical ventilation.

Preparation for Intubation

a. Standard preparation for rapid sequence intubation should include:
    - Cardio-respiratory and blood pressure monitoring, monitoring of oxygen saturation, careful aspiration of oropharynx, Bag and mask ventilation with 100 percent oxygen, Emptying of the stomach by nasogastric tube.
    - A benzodiazepine should be considered (e.g., midazolam 0.1-0.2 mg/kg) permitting relaxation during preoxygenation.
    - Use of sedatives is not recommended in children with status asthmaticus, except for intubation and mechanical ventilation.

b. Sedation and analgesia for intubation:
    - Ketamine hydrochloride (1 to 3 mg/kg) is a good choice for its sedative and analgesic effects as well as its bronchodilator properties. Concomitant use of a benzodiazepine can suppress the dysphoric effects of ketamine. However, ketamine increases laryngeal secretions but does not block pharyngeal and laryngeal reflexes, increasing the risk of laryngospasm and aspiration in the preintubation period.
    - Airway control and intubation can be facilitated by a short or intermediate acting neuromuscular blocking agents (vecuronium, rocuronium, or succinylcholine). Pancuronium should be avoided for its histamine release effect.

Endotracheal Intubation

Rapid sequence intubation should be performed by the most experienced operator.[16,17] Manipulation of the airway in the asthmatic child can worsen the bronchospasm or provoke a laryngospasm. Pretreatment with atropine and/or topical anesthetics at the level of the hypopharynx and glottis can possibly prevent these complications.

The largest endotracheal tube possible should be chosen to lower airflow resistance and permit suctioning of thick mucosal secretions. A cuffed endotracheal tube is sometimes useful even in small children (< 5 years) when insufflation pressures become very high.

Oral intubation is preferred in large children and is the method of choice due to the simplicity and speed of the procedure. After intubation, overenthusiastic bagging can result in hypotension or pneumothorax. To treat this hypotension due to hyperinflation, fluid boluses should be administrated quickly. The endotracheal tube could also be temporary disconnected from the ventilator or the anesthesia bag, allowing airway pressure to decrease.

Mechanical Ventilation

Tracheal intubation may worsen the bronchospasm and mechanical ventilation is associated with significantly greater mortality and morbidity in adults (as high as 40%) than in children (0-5%). Patients who have had previous life-threatening asthmatic attack or were admitted in hospital within the last year are at increased risk of mortality.

a. *Strategies for mechanical ventilation:* The goals of mechanical ventilation include choice of optimal ventilatory settings to effectively reduce dynamic hyperinflation (DHI), by limited minute ventilation (MV) using an appropriately low but adequate tidal volume (Vt) and respiratory rate, with an extended expiratory time (TE).

A strategy with tolerable level of gas exchange (permissive hypercapnia[18,19] with the lowest positive inspiratory pressure (PIP) and the lowest expiratory lung volume, avoiding intrinsic positive end expiratory pressure (PEEP) may be used. Intrinsic PEEP accumulates due to airway obstruction from bronchoconstriction. It could worsen DHI, barotrauma and air leak risks.[20]

On a graphics monitor of the ventilator DHI can be evaluated as follows:

1. *Elevated intrinsic PEEP:* failure of expiratory curve to return to the baseline before next inspiration.
2. *Elevated plateau pressure (Pplat):* Pplat is an average end inspiratory alveolar pressure. This pressure is determined by stopping flow at end-inspiration, allowing the peak pressure to fall to Pplat as resistive pressure falls to zero. A Pplat above 30 cm H_2O in adults has been correlated with complications. Specific pediatric studies are unavailable.
3. *Elevated end inspiratory volume (VEI):*[21,22] VEI can be measured by disconnecting sedated and relaxed patient from the ventilator. The apnea interval must be long enough (20 to 30 seconds) so that expiratory flow ceases. Total expired volume is the VEI. The difference between Vt and VEI is the volume of gas trapped in the lungs (VDHI). VEI must be less than 20 mL/kg/minute to reduce volu- and barotrauma risks.

Mode of Ventilation

No ventilation mode has been proved to be superior in status asthmaticus. Classically children are ventilated using volume controlled mode. This mode guarantees reproducible VT despite variations of airways resistance but then, the consequent rise of pressure must be limited.

In the pressure controlled mode, variations of resistance induce important variations of VT. A continuous monitoring of ventilation is always indicated (inspiratory and expiratory parameters of the ventilator, oxygen saturation, capnography, ABG).

Assisted and spontaneous mode are not indicated in the acute stage of status asthmaticus. As patient condition deteriorates, both increases in Vt or decreases in expiratory time increase the risk of DHI, though some authors suggest that assisted ventilation with elevated PEEP will decrease the work of breathing in asthma. However, an increased incidence of barotrauma in this mode of ventilation has been described.[23]

Pressure support ventilation[24] has been used in children with severe asthma. In this mode, ventilator just gives a flow (with a preset pressure limit) initiated by patient effort and the patient can determine the respiratory cycle, frequency and flow pattern. There is active exhalation and decreased end expiratory lung volume, plateau pressure falls, and barorauma decreases.

Initial Ventilator Settings

Suggested initial ventilator settings for the child with status asthmaticus could be:

Tidal volume: 6 to 8 mL/kg

Respiratory rate: I:E ratio of 1:3 to 1:4 (50% of usual respiratory rate for the child's age)

Inspiratory pause: None or minimal

PEEP: 2 to 3 cm H_2O (as long as less than auto PEEP as discussed earlier) Ventilation is maintained at the lowest level [i.e., small tidal volumes and long expiratory time with a low respiratory rate, with Pplat < 30 cm H_2O], allowing a relatively high PCO_2 (maximum 90 mmHg, without rapid rise) if oxygenation remains adequate (arterial saturation > 90%) and pH stays above 7.20 (with addition of sodium bicarbonate if necessary).

Risks of permissive hypercapnia include worsening of pre-existing intracranial hypertension (cerebral vasodilation and edema), myocardial depression and pulmonary vasoconstriction.

PEEP (Positive end expiratory pressure): Controversies remain about the role of PEEP in status asthmaticus. In the majority of cases, small PEEP may be applied during mechanical ventilation (3 cm H_2O) to decrease the risk of auto-PEEP, compromised venous return and cardiac output reduction. In adults, mechanical ventilation with high PEEP may be associated with a decrease in the work of breathing if the extrinsic PEEP is not higher than the intrinsic PEEP (< 10 cm H_2O).

Respiratory Care During Ventilation

Frequent suctioning of the endotracheal tube and bronchial tree should be performed to avoid plugging. Bronchoscopic lavage with acetylcysteine to remove plugs is sometimes recommended but may increase bronchospasm.

Aerosol Therapy in Ventilated Patients

It is possible to administer bronchodilators to intubated patients.[25-27] However, even if the delivery system is optimally assembled, lung deposition is influenced by a myriad of technical factors such as ventilator type, the delivery system itself, the ventilator circuit, ventilation mode, as well as numerous other individual parameters including the infectious status of the patient, thoracic volume alterations, fluid overload and other drugs administered. For these reasons, it is impossible to recommend any therapeutic regimen, but as a rule, one should administer supra-normal doses which should be adjusted according to clinical and physiological parameters. Both nebulizers or metered-dose inhalers can be used, according to individual choice and work load in the intensive care unit. To our knowledge, the comparative efficacy of inhaled versus intravenous bronchodilators in severe intubated asthmatic patients has never been evaluated.

Inhaled Anesthetic Agents

Inhaled anesthetic agents are known to relieve bronchospasm; diethylether and cyclopropane were used before the introduction of modern halogenated agents like halothane, isoflurane or enflurane. Today, halogenated gases are more commonly used in refractory status asthmaticus in mechanically ventilated patients.

Effects of halogenated agents in asthma are attributed to sustained bronchodilation, possibly by airway reflex blockade and a direct effect on smooth muscle.

Halothane/isoflurane have been used in patients with severe resistant bronchospasm while on ventilator. Both agents are potent bronchodilators. Myocardial depression and vasodilatation may occur with high concentrations.[28,29]

Knowledge of the properties, advantages and disadvantages of each gas is required for use in a PICU where anesthetists are not necessarily always present.

Anesthetic Potency

Minimal Alveolar Concentration (MAC) at which 50 percent of the recipients move, in response to incision, slightly less (10-20%) than the concentrations required for clinical use.

Equipotency in Halogenated Gas

1. MAC for Halothane = 0.75%
   Isoflurane = 1.15%
   Enflurane = 1.68%

In practice, the actual concentration of halogenated agents that must be delivered may vary considerably by factors that alter MAC (e.g., no neuromuscular blockers, low arterial pressure, morphine). Recovery from halothane may be delayed by the production of bromide from its metabolism. Recovery from isoflurane and enflurane is equally rapid.

Other Alternative Therapies

ECMO (veno-arterial or veno-venous): Extracorporeal membrane oxygenation would be to provide lung rest that would allow decompression of the hyperinflation. It has been used successfully in critical asthmatic children.

Heliox: An inert gas which has one-fourth the density of air. Mixtures of helium and oxygen (60-40%) decrease the work of breathing by decreasing inspiratory and expiratory resistance. The equipment to use is cumbersome and limited by maximum delivery of oxygen to be up to 40 percent.

Nitric oxide: Author has used it few times in obese asthmatic patients (severely hypoxemic despite ventilation) who had clinical evidence of pulmonary hypertension. Very few studies are available in this regard.

Sedation During Mechanical Ventilation

Morphine is not recommended in asthma due to its mast cell-mediated histamine release, potentially worsening bronchoconstriction. The following agents may be considered for sedation and analgesia in the child receiving mechanical ventilation for asthma:

Benzodiazepines (midazolam or diazepam) are anxiolytic and sedative but provide no analgesia.

Ketamine by continuous infusion or bolus is most frequently used. The safety of ketamine for long-term use is not well-established. Rock recommended a bolus of ketamine of 0.5 to 1 mg/kg IV over 5 minutes followed by 1 to 2.5 mg/kg/hour as a continuous infusion.[30,31]

Droperidol, an alpha-adrenergic antagonist, can also be used for maintenance of sedation and has been reported to have bronchodilating properties. Recommended doses are between 300 and 800 mg/kg divided in 3 to 4 doses a day.

Propofol as a continuous infusion may be associated with generalised seizures and hypertriglyceridemia and increased CO_2 and is not recommended for routine use in children.

Non-depolarizing neuromuscular blocking agents (vecuronium or atracurium) are frequently added to the sedation and analgesia to adequately assure patient-ventilator synchrony, improvement in thoracic compliance, the lowest peak inspiratory pressure (PIP) for adequate ventilation, and rest for the respiratory muscles.

If neuromuscular blockers are used for prolonged periods one should monitor neuromuscular status (e.g. with a train-of-four twitch monitor, titrating the blockade to two twitches, or by daily discontinuation of the muscle relaxant to evaluate the reversibility of paralysis).

Weaning from Mechanical Ventilation

When bronchoconstriction improves, dynamic hyper-inflation (DHI) and auto-PEEP will decrease. Oxygenation may actually worsen at this point, but should improve with the addition of a small amount of PEEP (4 to 6 cm H_2O). Neuromuscular blockade can be discontinued when the peak inspiratory pressure is less than 30 cm H_2O. Sedation is then tapered if arterial blood gases remain in the normal range ($PCO_2 < 45$ mm Hg and $PaO_2 > 70$ mm Hg with 50 percent oxygen maximum). The weaning period should be brief: A short T-Tube trial should precede a rapid extubation. A 'rapid sequence' for extubation is justified by the risk of further bronchoconstriction induced by the presence of the endotracheal tube in status asthmaticus.

Complications of Mechanical Ventilation

Mechanical ventilation in asthma is linked with several complications:

a. *Barotrauma and volume trauma:* Pneumothorax, pneumomediastinum, pneumoperitoneum and interstitial emphysema can occur.[32] These complications can be minimized if plateau pressure is adequately monitored and prolonged expiratory time is used.
b. *Hemodynamic instability:* After intubation, hypotension is commonly due to hyperinflation, hypovolemia and sedation. The treatment consists in rapid fluid bolus and modification of the ventilatory settings.

Other complications include: tissue hypoxia, arrhythmias, edema mucous plugs, atelectasis, nosocomial infection (pneumonia, sinusitis, other), and unventilable thorax.[33]

After intubation a perilous phase may ensue which is due to worsening of DHI (dynamic hyperinflation). Paralysis with nondepolarizing muscle relaxants suppresses the tonic part of hyperinflation (accessory muscles paralysis), and may cause a thorax to become unventilable due to aggravation of the obstructive syndrome.

Quick solutions to break this vicious circle (i.e. reducing hyperinflation) are:

- Transient use of a high PEEP (> 10 cm H_2O) with 100 percent oxygen, ventilation with a rate of 2 to 3 breaths per minute for several minutes.
- Acceleration of expiratory flow by manually compressing the rib cage, the patient being disconnected from ventilator.
- Other contributing causes of increased mortality are the inappropriate use of sedatives and complications of asthma medications (aminophylline or beta 2-agonists). In many cases, mortality and morbidity are related to cerebral anoxia occurring prior to hospital admission, and/or barotrauma.[34,35] The latter is now less frequent since the introduction of controlled alveolar hypoventilation.

Summary of Treatment of Acute Severe Asthma

Upon arrival to emergency room, after rapid cardiopulmonary assessment:

- Prompt initiation of oxygen therapy and
- Salbutamol nebulization (3 back to back treatments/4 to 8 puffs by inhaler/spacer)
- Adrenaline s/c 0.01 mg/kg can be used in addition if no response.
- Systemic glucocorticoid: Intravenous methylprednisolone 1-2 mg/kg hydrocortisone10mg/kg or IM route must be administered.

Reassessment at one hour:

- If good response: Discharge on inhaled β-2 agonist and oral steroids 3 to 10 days.
- If O_2 sat < 90, tachycardia, shallow fast breathing, altered sensorium: ADMIT to PICU:
  - Upon admission
  - Continue O_2
  - β-2 agonist inhalation every 20 min or continuous nebulization 0.5 mg/kg (max 15 mg/hr).

Intravenous (IV) $MgSO_4$, 50 per cent solution: 50 mg/kg/dose in 30 ml saline over 30 min may be considered.

Continue IV steroids, Oxygen, Continuous nebulization with salbutamol/terbutaline, Try-adrenaline s/c, IV $MgSO_4$, Ipratropium, beginIV steroids. If not improving and exhausted, lethargic, showing increasing mixed acidosis despite maximal oxygen, bronchodilator and steroid therapy.

Initiate mechanical ventilation with Low tidal volume, high expiratory time, plateau pressure monitoring. Nebulize β-2 agonists on ventilator, consider pressure support mode if feasible.

Theophylline has no role in acute asthma due to safer drugs availability. Use of halothane, heliox and ECMO should be reserved for patients deteriorating despite proper controlled ventilation.

Long acting β-2 agonists used with inhaled steroids (salmetrol with fluticasone) can be helpful *interval therapy only* after acute episode.

Ventilation is associated with potential risks of cardiac arrest during intubation, air leak such as pneumomediastinum and pneumothorax during ventilation as well as cardiac tamponade leading to cardiovascular collapse. However, if judiciously used to prevent dynamic hyperinflation, with adequate expiratory time, permitting a certain level of hypercapnia, and monitoring autopeep and plateau pressures, ventilation is an important life saving measure in children with acute life threatening asthma.

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APPENDIX

BRITISH THORACIC SOCIETY(BTS) GUIDELINES 2004 (ACUTE ASTHMA)

DIAGNOSIS OF ASTHMA IN CHILDREN

A definitive diagnosis of asthma can be difficult to obtain in young children. It is often not possible to measure airway function in order to confirm the presence of variable airway obstruction.

Asthma should be suspected in any child with wheezing, ideally heard by a health professional on auscultation, and distinguished from upper airway noises.

In school children, bronchodilator responsiveness, PEF variability or tests of bronchial hyperreactivity may be used to confirm the diagnosis, with the same reservations as in adults (Table app. 1).

Table app. 1: Diagnosis of asthma in children

Presenting features
- Wheeze
- Dry cough
- Breathlessness
- Noisy breathing

Detailed history and physical examination
- Pattern of illness
- Severity/control
- Differential clues

Is it asthma? Follow relevant course of action
Seek specialist assistance
Investigate or question to seek
- Causal factors
- Exacerbating factors
- Complications
- Comorbidity

Allergy tests may be helpful in seeking causal factors, and in making a general diagnosis of atopy.

The presence of allergy is not essential to the diagnosis of asthma, but its absence in a school child with symptoms suggestive of asthma should prompt consideration of alternative diagnoses.

Base the diagnosis of asthma in children on:

1. The presence of key features and careful consideration of alternative diagnoses (Table app. 2)
2. Assessment of the response to trials of treatment, and ongoing assessment.
3. Repeated reassessment of the child, questioning the diagnosis if management is ineffective.
4. Record the criteria on which the diagnosis has been made.

Indications for referral for specialist opinion. Further investigations in children

1. Diagnosis unclear or in doubt
2. Symptoms present from birth or perinatal lung problem
3. Excessive vomiting or posseting
4. Severe upper respiratory tract infection
5. Persistent wet cough
6. Family history of unusual chest disease
7. Failure to thrive
8. Unexpected clinical findings e.g. focal signs in the chest, abnormal voice or cry, dysphagia, inspiratory stridor
9. Failure to respond to conventional treatment, particularly inhaled corticosteroids above 400 mcg /day
10. Frequent use of steroid tablets
11. Parental anxiety or need for reassurance

Table app. 2: Clues to alternative diagnoses in wheezy children (features not commonly found in asthma)

Clinical clue Possible diagnosis
Perinatal and family history
Symptoms present from birth or perinatal cystic fibrosis;
chronic lung disease; lung problem ciliary dyskinesia;
developmental anomaly
Family history of unusual chest disease cystic fibrosis;
developmental anomaly; neuromuscular disorder
Severe upper respiratory tract disease Defect of host
defence
Symptoms and signs
Persistent wet cough cystic fibrosis; recurrent aspiration;
host defence disorder
Excessive vomiting or posseting reflux (± aspiration)
Dysphagia swallowing problems (± aspiration)
Abnormal voice or cry laryngeal problem
Focal signs in the chest Developmental disease; postviral
syndrome; bronchiectasis, tuberculosis
Inspiratory stridor as well as wheeze Central airway or
laryngeal disorder
Failure to thrive Cystic fibrosis; host defence defect;
gastro-oesophageal reflux
Investigations
Focal or persistent radiological changes Developmental
disorder; postinfective disorder; recurrent aspiration;
inhaled foreign body; bronchiectasis; tuberculosis

PROGNOSIS OF CHILDHOOD ASTHMA

Therapeutic decisions, particularly the introduction of prophylactic treatments may be influenced not only by the presence of persistent symptoms but by current understanding of the pathophysiology and the natural history of the disease.

If the factors associated with resolution and persistence of asthma presenting in childhood were not taken into account and every child presenting with wheeze was treated prophylactically, half of all children would be treated.

The major identifiable risk factors contributing to both the expression and persistence of asthma are considered in the following section:

A. FAMILY HISTORY OF ATOPY

A family history of atopy is the most important clearly defined risk factor for atopy in children.

Asthma is linked to both parental and sibling atopy. The strongest association is with maternal atopy. A maternal history of asthma and/or rhinitis is a significant risk factor for late childhood onset asthma and recurrent wheezing throughout childhood. The association of persistence of symptoms with maternal asthma and rhinitis weakens during the transition to adulthood.[1-4]

B. CO-EXISTENCE OF ATOPIC DISEASE

Markers of allergic disease at presentation, (including skin prick tests, eosinophil counts and peripheral blood markers), are related to severity of current asthma and persistence through childhood, but as yet have not been shown to be related to the outcome of respiratory symptoms and their severity in adulthood.[1-14]

C. EFFECT OF SEX

Male sex is a risk factor for asthma in prepubertal children and female sex is a risk factor for persistence of asthma in the transition from childhood to adulthood. Male children with asthma are more likely to .grow out of their asthma in the transition to adulthood.[1,3,8,24-31]

D. BRONCHIOLITIS IN INFANCY

Viral associated wheeze in infancy is often followed by wheeze in early childhood. This association weakens with advancing age and by 35-40 years ventilatory function and bronchial reactivity are similar to those who had no symptoms as children.[2,10,15-23]

E. PARENTAL SMOKING

Maternal smoking is associated with significantly higher prevalence of wheezing illness in early childhood. However, there is no identifiable association between parental smoking and respiratory symptoms in adult life. Reducing the prevalence of smoking in the adult population, and particularly in women of childbearing age, would significantly reduce the prevalence of wheezing in young children.[1,3,8,24-31]

F. BIRTH WEIGHT AND PREMATURITY

Wheezing is more common in young children who were born prematurely. In adulthood there are no consistent relationships between asthma and birth weight.[16,24,29,30,32,33]

G. AGE AT PRESENTATION

The natural history of wheeze is dependent on the age at first presentation. The earlier the onset of wheeze, the better the prognosis. Available data from child cohorts show a break point at two years with the majority of those presenting before this age becoming asymptomatic by mid childhood (6-11 years). It must be remembered that coexistent atopy is a risk factor for persistence independent of age of presentation.[1,5,6,10,14,19,34-39]

H. SEVERITY AND FREQUENCY OF EPISODES

Increased frequency and severity of wheezing episodes in childhood are associated with recurrent wheeze into adulthood.[1,5,6,11,13,34,38,40,41,42,43]

I. LUNG FUNCTION MEASUREMENTS

There is a relationship between the level of pulmonary function in childhood and in adulthood.

Persistent reduction in baseline airway function and increased airway responsiveness is associated with continuation of symptoms into adulthood. [1,2,12,18,34,42,44-46]

ACUTE ASTHMA IN CHILDREN AGED OVER 2 YEARS

Initial Assessment

Table app. 3 details criteria for assessment of severity of acute asthma attacks in children.

Table app. 3: Clinical features for assessment of severity

Acute severe life threatening

Can't complete sentences in one breath n Silent chest

or too breathless to talk or feed n Cyanosis

- Poor respiratory effort
  Pulse >120 in children aged >5 years
  >130 in children aged 2-5 years n Hypotension
- Exhaustion
  Respiration >30 breaths/min aged >5 years
- Confusion
  >50 breaths/min aged 2-5 years
- Coma
  Before children can receive appropriate treatment for acute asthma in any setting, it is essential to assess accurately the severity of their symptoms. The following clinical signs should be recorded:
- Pulse rate (increasing tachycardia generally denotes worsening asthma; a fall in heart rate in life threatening asthma is a pre-terminal event).
- Respiratory rate and degree of breathlessness (i.e. too breathless to complete sentences in one breath or to feed).
- Use of accessory muscles of respiration (best noted by palpation of neck muscles).

contd...

contd...

- **Amount of wheezing (which might become biphasic or less apparent with increasing airways obstruction).**
- **Degree of agitation and conscious level (always give calm reassurance).**

Clinical signs correlate poorly with the severity of airways obstruction.[47-50] Some children with acute severe asthma do not appear distressed.

Objective measurements of PEF and SpO_2 are essential. Suitable equipment should be available for use by all health professionals assessing acute asthma in both primary and secondary care settings.

Low oxygen saturations after initial bronchodilator treatment selects a more severe group of patients.[47-50]

B Consider intensive inpatient treatment for children with SpO_2 <92% on air after initial bronchodilator treatment.

- Decisions about admission should be made by trained physicians after repeated assessment of the response to further bronchodilator treatment.
  A measurement of <50% predicted PEF or FEV1 with poor improvement after initial bronchodilator treatment is predictive of a more prolonged asthma attack.
- Attempt to measure PEF or FEV1 in all children aged >5 years, taking the best of three measurements, ideally expressed as percentage of personal best for PEF (as detailed in a written action plan) or alternatively as percentage of predicted for PEF or FEV1.

Chest x-rays and ABG measurements rarely provide additional useful information and are not routinely indicated.[51,52]

TREATMENT OF ACUTE ASTHMA IN CHILDREN AGED OVER 2 YEARS

Emergency units attending to children with acute asthma should have a registered sick children's nurse available on duty at all times and staff familiar with the specific needs of children. The use of proformas can increase the accuracy of severity assessment.

An assessment-driven algorithm has been shown to reduce treatment costs and hospital stay.

The use of structured care protocols detailing bronchodilator usage, clinical assessment, and specific criteria for safe discharge is recommended.

A. OXYGEN

- Children with life threatening asthma or SpO_2 <92% should receive high flow oxygen via a tight fitting face mask or nasal cannula at sufficient flow rates to achieve normal saturations.

B. BETA 2 AGONIST BRONCHODILATORS

A Inhaled b2 agonists are the first line treatment for acute asthma.

pMDI + spacer is an effective alternative to nebulizers bronchodilator inhalation to treat mild to moderate asthma. Children receiving b2 agonists via pMDI + spacer are l likely to have tachycardia and hypoxia than when the sa drug is given via a nebulizer.[54]

A pMDI + spacer are the preferred option in mild moderate asthma.

Information about implementing evidence-bas guidelines using such devices has been published.[56] Child aged <3 years are likely to require a face mask connecte the mouthpiece of a spacer for successful drug delive Inhalers should be actuated into the spacer in individual p and inhaled immediately by tidal breathing.

Frequent doses of b2 agonists are safe for the treatmen acute asthma,[56-58] although children with mild sympto benefit from lower doses.[59]

Individualise drug dosing according to severity and adj according to the patients response.

Two to four puffs repeated every 20-30 minutes accord to clinical response might be sufficient for mild atta although up to 10 puffs might be needed for more sev asthma.

Children with acute asthma in primary care who have improved after receiving up to 10 puffs of b2 agonist sho be referred to hospital. Further doses of bronchodilator sho be given as necessary whilst awaiting transfer.

Treat children transported to hospital by ambulance w oxygen and nebulised b2 agonists during the journey.

Transfer children with severe or life threatening asth urgently to hospital to receive frequent doses of nebulised agonists (2.5-5 mg salbutamol or 5-10 mg terbutaline).

Doses can be repeated every 20-30 minutes. Continu nebulised b2 agonists are of no greater benefit than the use frequent intermittent doses in the same total hourly dosage [61]

C. IV SALBUTAMOL

The role of intravenous b2 agonists in addition to nebulis treatment remains unclear.[62] One study has shown that an bolus of salbutamol given in addition to near maximal do of nebulised salbutamol results in clinically signific benefits.[62]

The early addition of a bolus dose of intraven salbutamol (15 mcg/kg) can be an effective adjunct treatment in severe cases.

Continuous intravenous infusion should be conside when there is uncertainty about reliable inhalation or severe refractory asthma. Doses above 1-2 mcg/kg/min (mcg/ml solution) should be given in a Paediatric Intens Care Unit (PICU) setting (up to 5 mcg/kg/min) with regu monitoring of electrolytes.

D. STEROID THERAPY

Steroid tablets

The early use of steroids for acute asthma can reduce need for hospital admission and prevent a relapse symptoms after initial presentation.[63,64] Benefits can be apparent within three to four hours.

Give prednisolone early in the treatment of acute asthma attacks.

A soluble preparation dissolved in a spoonful of water is preferable in those unable to swallow tablets. Use a dose of 20 mg for children 2-5 years old and 30-40 mg for children >5 years.

Oral and intravenous steroids are of similar efficacy.[65-67] Intravenous hydrocortisone (4 mg/kg repeated four hourly) should be reserved for severely affected children who are unable to retain oral medication.

Larger doses do not appear to offer a therapeutic advantage for the majority of children. There is no need to taper the dose of steroid tablets at the end of treatment.

- Use a dose of 20 mg prednisolone for children aged 2-5 years and a dose of 30-40 mg for children >5 years. Those already receiving maintenance steroid tablets should receive 2 mg/kg prednisolone up to a maximum dose of 60 mg.
- Repeat the dose of prednisolone in children who vomit and consider intravenous steroids in those who are unable to retain orally ingested medication.
- Treatment for up to three days is usually sufficient, but the length of course should be tailored to the number of days necessary to bring about recovery.

Inhaled steroids

There is insufficient evidence to support the use of inhaled steroids as alternative or additional treatment to steroid tablets for acute asthma.[68-71]

- Do not initiate inhaled steroids in preference to steroid tablets to treat acute childhood asthma.

Children with chronic asthma not receiving regular preventive treatment will benefit from initiating inhaled steroids as part of their long term management. There is no evidence that increasing the dose of inhaled steroids is effective in treating acute symptoms, but it is good practice for children already receiving inhaled steroids to continue with their usual maintenance doses.

E. IPRATROPIUM BROMIDE

There is good evidence for the safety and efficacy of frequent doses of ipratropium bromide used in addition to b2 agonists for the first two hours of a severe asthma attack. Benefits are more apparent in the most severe patients.[72]

If symptoms are refractory to initial b2 agonist treatment, add ipratropium bromide (250 mcg/dose mixed with the nebulised b2 agonist solution).

Frequent doses up to every 20-30 minutes (250 mcg/dose mixed with the b2 agonist solution in the same nebuliser) should be used early. The dose frequency should be reduced as clinical improvement occurs.

- Repeated doses of ipratropium bromide should be given early to treat children poorly responsive to b2 agonists.

Children with continuing severe asthma despite frequent nebulised b2 agonists and ipratropium bromide and those with life threatening features need urgent review by a specialist with a view to transfer to a High Dependency Unit or PICU.

F. IV AMINOPHYLLINE

There is no evidence that aminophylline is of benefit for mild to moderate asthma and side effects are common and troublesome.[73,74] However, one well conducted study has shown evidence for benefit in severe acute asthma unresponsive to multiple doses of b2 agonists and steroids.[75]

Aminophylline is not recommended in children with mild to moderate acute asthma.

Consider aminophylline in a High Dependency Unit or PICU setting for children with severe or life threatening bronchospasm unresponsive to maximal doses of bronchodilators and steroid tablets.

A 5 mg/kg loading dose should be given over 20 minutes with ECG monitoring (omit in those receiving maintenance oral theophyllines) followed by a continuous infusion at 1 mg/kg/hour.

Estimate serum theophylline levels in patients already receiving oral treatment and in those receiving prolonged treatment.

G. OTHER THERAPIES

There is no evidence to support the use of heliox or leukotriene receptor antagonists for the treatment of acute asthma in childhood.

There is insufficient evidence to support or refute the role of antibiotics in acute asthma, but the majority of acute asthma attacks are triggered by viral infection.

- Do not give antibiotics routinely in the management of acute childhood asthma.

H. INTRAVENOUS FLUIDS

Children with prolonged severe asthma not tolerating oral fluids will require intravenous hydration.

Two thirds of the child's maintenance requirement should be given because of the possibility of inappropriate antidiuretic hormone secretion. Serum electrolytes should be measured and hypokalaemia corrected if detected. ECG monitoring is mandatory for all intravenous treatments.

I. IV MAGNESIUM SULPHATE

Intravenous magnesium sulphate is a safe treatment for acute asthma although its place in management is not yet established.[76,77] Doses of up to 40 mg/kg/day (maximum 2g) by slow infusion have been used. Studies of efficacy for severe childhood asthma unresponsive to more conventional therapies have been inconsistent in providing evidence of benefit.

FURTHER INVESTIGATION AND MONITORING

Children can be discharged when stable on 3-4 hourly inhaled bronchodilators that can be continued at home. PEF and/or FEV1 should be >75% of best or predicted and SpO_2 >94%.

Adult studies show that .optimal care. comprising self-monitoring, regular review and a written asthma action plan can improve outcomes.[78] Acute asthma attacks should be considered a failure of preventive therapy and thought should be given about how to help families avoid further severe episodes. Discharge plans should address the following:

- Check inhaler technique
- Consider the need for regular inhaled steroids
- Provide a written asthma action plan for subsequent asthma with clear instructions about the use of bronchodilators, seeking urgent medical attention in the event of worsening symptoms and, if appropriate, starting a course of oral steroids
- Arrange follow up by a GP within one week
- Arrange follow up in a paediatric asthma clinic within one to two months.

ASSESSMENT OF ACUTE ASTHMA IN CHILDREN AGED LESS THAN 2 YEARS

The assessment of acute asthma in early childhood can be difficult. Intermittent wheezing attacks are usually due to viral infection and the response to asthma medication is inconsistent. Prematurity and low birth weight are risk factors for recurrent wheezing. The differential diagnosis of symptoms includes aspiration pneumonitis, pneumonia, bronchiolitis, tracheomalacia, and complications of underlying conditions such as congenital anomalies and cystic fibrosis. These guidelines are intended for those who are thought to have asthma causing acute wheeze. They should not be used as a guide for treating acute bronchiolitis.

TREATMENT OF ACUTE ASTHMA IN CHILDREN AGED LESS THAN 2 YEARS

A. Beta 2 Agonist Bronchodilators

A trial of bronchodilator therapy should be considered when symptoms are of concern. If inhalers have been successfully administered but there is no response, review the diagnosis and consider the use of other treatment options.

Oral b2 agonists have not been shown to affect symptom score or length of hospital stay for acute asthma in infancy when compared to placebo.[79]

Oral b2 agonists are not recommended for acute asthma in infants.

Inhaled b2 agonists are the treatment of choice for the initial treatment of acute asthma. Close fitting face masks are essential for optimal drug delivery. The dose received is increased if the child is breathing appropriately and not taking large gasps because of distress and screaming.

There is good evidence that pMDI + spacer is as effective as, if not better than, nebulisers for treating mild to moderate asthma in children aged <2 years.[80-82]

For mild to moderate acute asthma, a pMDI + spacer is the optimal drug delivery device.

Whilst b2 agonists offer marginal benefits to children aged <2 years with acute wheeze, there is little evidence for an impact on the need for hospital admission or length of hospital stay.[80-82]

B. Steroid Therapy

Steroid tablets in conjunction with b2 agonists have been shown to reduce hospital admission rates when used in the emergency department. Steroid tablets have also been shown to reduce the length of hospital stay.[79,80,83]

Consider steroid tablets in infants early in the management of moderate to severe episodes of acute asthma in the hospital setting.

One study has shown similar benefits when comparing oral and nebulized steroids for acute asthma.[80]

Steroid tablet therapy (10 mg of soluble prednisolone for up to three days) is the preferred steroid preparation for use in this age group.

C. Ipratropium Bromide

The addition of ipratropium bromide to b2 agonists for acute severe asthma may lead to some improvement in clinical symptoms and reduce the need for more intensive treatment. It does not reduce the length of hospital stay either in combination with b2 agonists or in comparison with placebo.[84]

Consider inhaled ipratropium bromide in combination with an inhaled b2 agonist for more severe symptoms.

FURTHER INVESTIGATION AND MONITORING

Many children with recurrent episodes of viral-induced wheezing in infancy do not go on to have chronic atopic asthma. The majority do not require treatment with regular inhaled steroids.

Parents should be advised about the relationship between cigarette smoke exposure and wheezy illnesses. Referral to suitable agencies should be offered to those who wish to give up smoking.

Parents of wheezy infants should receive appropriate discharge plans along similar lines to those given for older children .

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CHAPTER

23

Viral Pneumonias: Common Pneumonias and Recent Advances

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SECTION 1 : COMMON VIRAL PNEUMONIAS

INTRODUCTION

World-wide, pneumonia is estimated to cause the deaths of 4 million children under 5 years annually.[1] Most of these deaths occur in the non industrialized world where bacterial organisms are largely responsible.[2] However, in industrialized countries, where mortality is much lower, viruses account for most lower respiratory infections. In a recent survey of children admitted to hospital with pneumonia, 75 percent of infections diagnosed were viral or 'atypical' infections (Mycoplasma or Chlamydia).[3] In the industrialized world, a great reduction in mortality from childhood pneumonia has been achieved in the last 60 years. In the US, deaths from pneumonia in children have fallen by 97 percent since 1939.[4]

Many children with viral lower respiratory infection present clinically with bronchiolitis. However, there may be typical features of pneumonia and it is often impossible to distinguish clinically or radiologically between viral and bacterial pneumonia.[3] Viruses such as influenza can directly infect the lower respiratory tract but can also predispose to a secondary bacterial bronchopneumonia.

One third of patients with bacterial pneumonia also harbor a virus known to cause pneumonia.

The clinical presentation of viral lower respiratory infection may be very atypical. For instance, post mortem evidence shows that children dying from sudden infant death syndrome more frequently have histological evidence of viral pneumonia than controls.[5]

Viral or atypical organisms may lead to a more severe form of pneumonia in the following groups: (i) bronchopulmonary dysplasia; (ii) immune deficiency or immunosuppression; (iii) congenital heart disease; (iv) asthma; and (v) cystic fibrosis and other disorders of mucociliary clearance such as primary ciliary dyskinesia.

Although it is difficult to distinguish clinically between viral and bacterial causes of pneumonia, inflammatory markers may be helpful.

Recent work suggests that one such marker, procalcitonin, has a similar sensitivity to C reactive protein (sensitivity 86%) but is more specific for bacterial pneumonia in children (specificity 88%).[6] This is a controversial question, with one estimate of the sensitivity of procalcitonin as low as 50 percent.[7] However, a low sensitivity may be due to children receiving prior treatment with antibiotics.

Immunofluorescence of respiratory secretions (e.g. nasopharyngeal aspirate, tracheal aspirate or broncho-alveolar lavage) can be performed against a 'panel' of respiratory viruses and is highly specific. This offers the possibility of near patient testing and early treatment with specific antiviral agents such as the neuraminidase inhibitors against influenza. The use of the polymerase chain reaction (PCR) can increase the rate of diagnosis of treatable causes of pneumonia from 13 to 31 percent.[3]

SPECIFIC VIRAL PATHOGENS AND THEIR CLINICAL SYNDROMES

Influenza

Influenza viruses of types A, B and C cause disease in man. Type A is responsible for influenza pandemics and can cause severe disease in the young. Types B and C do not cause pandemics and cause less severe disease.

Influenza virus maintains its infectivity in the community by undergoing **antigenic drift and shift**, due to changes in the protein structure of hemaglutinin. In the case of antigenic drift, these changes consist of a small number of amino acid substitutions only. When non-immune individuals encounter the modified virus, this leads to an epidemic. Less frequently, a much greater change in the antigenic structure of the virus occurs, with many more susceptible individuals in the community. This is called antigenic shift and leads to pandemics of influenza where many young adults are affected.

During an epidemic season, influenza can account for an excess of 19 admissions per 1000 infants at high risk.[8] Influenza can cause severe infection in patients with cystic fibrosis, although chest radiograph abnormalities are mainly those of bronchiectasis and sputum retention. Children immunosuppressed following transplantation are also vulnerable.[9]

Influenza is spread by aerosol transmission. Particles of up to 10 microns in diameter are most effective. The presence of specific secretary IgA antibodies to influenza, on the nasal mucosa, is protective. Infection leads to cell death, primarily in the upper airway. Direct viral infection of the lung parenchyma occurs, characterized by hemorrhage and a relative lack of inflammatory cells. Influenza virus has specific effects which may lead to secondary bacterial infection. Mucociliary clearance is impaired and bacterial adherence to respiratory epithelium is enhanced. Furthermore, influenza infection impairs T-cell, neutrophil and macrophage function.[10]

Influenza has an incubation period of 18-72 hours. The child may present with fever, myalgia and rigors. Fever usually lasts for around 3 days. Cough and pharyngitis are usually present initially, but may be overshadowed by the systemic symptoms. Younger children may develop croup. In children with a primary viral pneumonia, the fever may fail to settle and the cough becomes more prominent. In contrast, where influenza is complicated by bacterial pneumonia, the fever may settle initially,but then recur.

Influenza may be diagnosed by direct immunofluorescence or viral culture of respiratory secretions. Retrospectively, paired acute and convalescent serology, using the complement fixation test can be helpful. A 4-fold rise in titre between the acute and convalescent specimens is diagnostic.

Influenza vaccine is recommended for all patients with chronic respiratory disease.[11] This includes children with cystic fibrosis and asthma. The vaccine is usually given in an inactivated parenteral form, though a live aerosolized form has been developed. The parenteral form has an efficacy of 68 percent in the prevention of serologically proven influenza in healthy adults. Rates of hospitalization and complications such as pneumonia are not affected by immunization.[12] There is no evidence that immunization reduces the frequency of exacerbations in patients with asthma[13] or cystic fibrosis.[14]

Amantadine has been available for many years. It is only effective against influenza A. The license extends to children, although the appropriate dose for children under 10 years is unclear.

Zanamivir is the first of a new class of antiviral drugs-the neuraminidase inhibitors-to receive a license. Zanamivir is not absorbed when given orally and so inhalation is used. It shortens the duration of influenza symptoms by approximately 24 hours.[15] A reduction in complications such as pneumonia has not been demonstrated. In the UK, the National Institute for Clinical Excellence (NICE) has recommended the use of zanamivir for at-risk adults during an influenza epidemic, provided they present within 36 hours of the onset of symptoms and can start treatment within 48 hours.[16]

Long-term sequele of influenza are thought to be less common than with adenovirus pneumonia. However, bronchiectasis and obliterative bronchiolitis have been reported, when influenza infection occurs in the preschool child.[16]

Adenovirus

Organisms of the adenovirus sub-genera B, C, E and F cause respiratory and enteric infection in children. The virion can interact with the host cell in one of three ways. The reproductive cycle of the virus may be completed, leading to cell lysis and death. Alternatively, the virus may cause chronic infection in tissues such as the tonsil. In experimental animals, oncogenic transformation may occur when adenovirus. DNA is incorporated in the host cell genome.

Adenovirus is thought to cause around 10 percent of respiratory disease in children , though infection may be subclinical. In young adults, the incubation period is 4-5 days. The spectrum of illness varies from mild pharyngitis and tracheitis in older children and adults to severe bronchiolitis in infants. Extra pulmonary disease such as conjunctivitis, gastroenteritis, intussusception, hemorrhagic cystitis and encephalitis can occur. Children may have both respiratory and non-respiratory disease as a feature of their illness. Fatal adenovirus pneumonitis has been reported in transplant recipients.[17]

There is no antiviral agent of proven efficacy against adenovirus, though the use of intravenous ribavirin has been reported.[18] Specific immunoglobulin has been used in adenovirus infection, complicating severe combined immune deficiency.[16]

A live oral vaccine is available, but its use is restricted to military recruits in the UK.

Adenovirus may be cultured from throat swab, stool, conjunctival scrapings and urine. Rapid identification (though not serotyping) from respiratory secretions is possible by immunofluorescence. Serological diagnosis may be helpful retrospectively.

Adenovirus DNA has been found in the respiratory secretions of infants who develop bronchopulmonary dysplasia more frequently than in those with normal lungs.[19] This has led to speculation that it may have an etiological role in the development of bronchopulmonary dysplasia.

Pulmonary infection with adenovirus serotypes 3, 7 and 21 can lead to the development of obliterative bronchiolitis which may be accompanied by traction bronchiectasis. This is best diagnosed on high resolution computerized tomography (CT), where patchy areas of hyperinflation on the expiratory film produce the so-called 'mosaic' appearance.

Bronchiectasis may occur in over a quarter of children with adenovirus pneumonia.[20]

In one study, adenovirus DNA was demonstrated, by the PCR, in the respiratory secretions of 78 percent of children with stable asthma.[19] In contrast, adenovirus DNA was found in only one control patient. This has led to speculation that the chronic form of infection described above may have a role in the etiology of asthma.

Parainfluenza

Parainfluenza virus type 3 is endemic throughout the year, with a peak in spring; types 1 and 2 cause autumn epidemics. The virus shows a tropism for the ciliated epithelial cells, lining the large airways. Release of the virus, following replication, occurs from the apex of the cells into the mucus layer. The presence of a fusion protein can lead to formation of a syncytium of epithelial cells, as with RSV.

In a similar fashion to RSV, parainfluenza type 3 causes respiratory infection in infants under 6 months, who have maternally-derived antibody. Commonly, these infants present with bronchiolitis. In older children, croup is the most common clinical syndrome.

Pneumonia is uncommon in healthy children. However, fatal pneumonia, with viral dissemination, has been reported (with type 3) in a child with severe combined immune deficiency.[21] Bone marrow transplant patients are also vulnerable, with pneumonia developing in almost half of patients in whom the virus is isolated.[22] Children with bronchopulmonary dysplasia, prematurity, congenital heart disease or asthma are also more likely to develop lower respiratory infection and to require more supportive therapy . Secondary bacterial infection is thought to occur in approximately one-third of children with lower respiratory infection due to parainfluenzal.[23]

Rapid diagnosis and assignment to type 1, 2 or 3 is possible by immunofluorescence of respiratory secretions. Viral culture and paired sera may also be helpful.

No specific antiviral agent has been shown to be effective, though intravenous ribavirin has been used in the immunosuppressed.[24] A live attenuated nasal vaccine is being developed.[25]

Long-term sequelae of parainfluenza infection is uncommon. However, bronchiolitis obliterans with organizing pneumonia has been reported.[26]

Rhinovirus

One hundred rhinovirus immunotypes have been demonstrated and so individuals remain susceptible to new antigenic variants throughout life. Transmission is through the presence of infectious secretions on hands, with transfer to conjunctiva or nasal mucosa.

Rhinovirus grows best at temperatures of around 33° C and so it preferentially infects the nasal mucosa (which is cooled by inspired air). However, rhinovirus infection can trigger lower respiratory illness, particularly exacerbations of asthma. A community Southampton, UK, found that viruses, primarily rhinovirus, were found in 80 percent of reported episodes of wheeze, in school-aged children with asthma.[27] The mechanism of this effect has been the subject of much research interest. Biopsy studies have shown that there are increased numbers of bronchial lymphocytes and eosinophils, following experimental infection in volunteers.[28]

Other vulnerable groups may develop lower respiratory symptoms. In a prospective study of children with cystic fibrosis, 28 percent of exacerbations were associated with a viral infection, over half of which were rhinovirus.[29] Infants with bronchopulmonary dysplasia may also have a severe lower respiratory illness with rhinovirus. One study found that the frequency of intensive care admission was similar with rhinovirus and RSV, though fewer infants with rhinovirus needed ventilations.[30]

Immunofluorescence and serology are not available for diagnosis of rhinovirus infection as the large number of antigenic types makes this impracticable. Infection may be diagnosed by means of tissue culture of respiratory secretions at 33°C.

Nosocomial infection can be prevented by careful hand washing and this is important for those caring for vulnerable children in hospital. The prospects for a vaccine have been limited by the large number of serotypes.

Measles

Measles is one of the most contagious of the communicable diseases and is spread by direct contact with respiratory secretions. Children with measles are most infectious during the late prodromal phase and cease to be infectious 48 hours after the appearance of the rash. The introduction of immunization has resulted in a dramatic reduction in the incidence of infection in the UK, although sporadic outbreaks in non-immunized groups do occur.[31]

The virus can infect respiratory epithelium in the upper or lower respiratory tract.

The incubation period is 10-14 days. There follows a prodromal phase of fever, coryza and extreme misery. Towards the end of the prodrome, Koplick's spots appear on the mucosa on the inside of the cheek, followed shortly afterwards by a erythematous maculopapular rash.

Respiratory involvement is universal, and acute respiratory complications include laryngotracheobronchitis, bronchiolitis and measles-associated pneumonia. Measles pneumonia can result from direct viral invasion of the respiratory tract or from secondary infection with other bacteria or viruses. Both disruption of mucosal surfaces and the immuno suppression associated with measles virus, predispose to secondary infection which is thought to occur in over half of children with measles associated pneumonia.[32] Streptococcus pneumoniae is the commonest secondary bacterial infection, whilst parainfluenza and adenovirus are the most frequent viruses. During recovery from measles, cell-mediated immunity is suppressed. Measles infection is known to be associated with the later development of bronchiectasis.[33]

Diagnosis is usually made clinically. However, immunofluorescence of nasal secretions and PCR will both provide a rapid confirmation. Serological tests including complement fixation, hemagglutination inhibition and ELISA are helpful, where a rising titer can be demonstrated.

As bacterial secondary infection is common, routine antibiotic treatment for all children with measles has been practiced in many endemic regions. However, this practice is not supported by a recent Cochrane Review of studies (most of poor methodological quality) in over 1400 children with measles. This review found no difference in mortality, in children treated with antibiotics, compared to controls.[34]

Treatment with vitamin A has been shown to be beneficial, although children with measles may not have clinical evidence of vitamin A deficiency.

vitamin A 200,000 IU given orally, once daily for 2 days reduces the risk of death from measles by 64 percent.[35] Recovery from pneumonia is more rapid and fewer children develop laryngotracheobronchitis.[36]

Measles immunization is highly effective in preventing measles and reduces mortality in immunized children by between 40-75 percent.[37] However, paradoxically, when deaths from measles are excluded, this reduction is virtually unchanged. This suggests that immunization has a non-specific beneficial effect, perhaps through immune sensitisation.

Cytomegalovirus (CMV)

CMV is a DNA virus — one of the largest viruses to infect man. CMV infection may present as a pneumonitis. In otherwise healthy individuals (usually young adults), this may occur as a complication of CMV mononucleosis and causes only mild symptoms. However, in immunosuppressed patients, such as renal transplant recipients,[38] the infection can have a significant mortality.

CMV antigen can be demonstrated in peripheral blood mononuclear cells by means of immunofluorescence and allows rapid diagnosis. PCR can be used to detect CMV DNA in body fluids. Culture of urine and broncho-alveolar lavage specimens may be diagnostic, though gives less rapid results.

Ganciclovir and foscarnet are effective, though toxic, antiviral agents. Where possible, transplanting CMV-positive donor organs or bone marrow to a CMV-negative recipient should be avoided.

Epstein-Barr virus (EBV)

EBV is a double stranded DNA virus, approximately 200 nm in diameter, surrounded by an envelope. By early adulthood, over 90 percent of healthy individuals will have serological evidence of past EBV infection.

Pulmonary manifestations of EBV in otherwise healthy individuals are rare. Dramatic tonsillar enlargement can lead to severe upper airways obstruction. In patients with cystic fibrosis, EBV has been shown to cause a deterioration in nutrition and pulmonary function which lasts over 6 months after diagnosis of the infection.[39]

The glandular fever screening test, which detects heterophile antibodies, is readily available and is positive in 90 percent of cases.

Varicella (Chicken pox)

Like CMV and EBV, varicella is a herpes virus. It is an enveloped DNA virus 150-200 nm in diameter.

Infection is usually mild when it occurs in early childhood. Hospitalization of children with varicella is rarely necessary. In the small number of children severe enough to be admitted to hospital, pneumonitis is common.[40] In the immunosuppressed, varicella can be associated with life threatening multiorgan involvements. In children with cystic fibrosis, pulmonary exacerbation can occur, without the typical radiological appearances of varicella. The deterioration in pulmonary function can take up to 18 months to resolve.[41]

Severe infection should be treated with intravenous acyclovir. Immunization is now available, but is not part of the primary immunization schedule and is currently optional.

SPECIFIC ATYPICAL PATHOGENS AND THEIR CLINICAL SYNDROMES

Mycoplasma Pneumoniae and Ureaplasma Urealyticum

The mycoplasmas are among the smallest free-living organisms which are pathogenic in man. They are deformable rods which pass through bacterial filters and are not seen on Gram staining.

Although infection is endemic in most communities, epidemics occur in 4-7 year cycles. School children are primarily affected.[42] There is an autumn peak, thought to correspond to children returning to school. Ureaplasma urealyticum is found in the female genital tract and can cause respiratory infection in the new-born. An association between respiratory infection with *U. urealyticum* and the development of chronic lung disease of prematurity has been demonstrated in studies, performed over a decade apart.[43,44] This is in spite of many innovations in neonatal care. Morbidity due to this infection is seen throughout the first year of life.[45]

Mycoplasma can be isolated from children with asthma more frequently than controls and mycoplasma has been suggested as a precipitating factor for a wheeze.[46] Prevalence in children with CF is low, possibly related to difficulties in isolating the organism in the presence of other pathogens.[47] Severe infection has been reported in Down's syndrome.[48]

The incubation period for *M. pneumoniae* is 2-3 weeks. Classically, a dry cough develops over 1-2 days, with low grade fever. The cough may be debilitating and can be confused with pertussis. Chest pain can occur Younger children may have upper respiratory infection only. Where pneumonia develops, clinical examination may be unremarkable. Classically, diffuse involvement on the chest radiograph is described. However, in a study of children admitted to hospital with pneumonia, most children with mycoplasma had lobar consolidation on chest radiograph.[3] Mycoplasma was the commonest single pathogen causing pneumonia in this study.

Traditionally, cold agglutinins are used for rapid diagnosis.[49] These are not specific for mycoplasma infection as they occur also in CMV and EBV infection. Neither are they 100 percent sensitive. Complement fixation tests are helpful retrospectively. New techniques such as PCR can be applied to blood or nasal secretions.[3] However, it may be necessary to combine PCR and serology to achieve maximum sensitivity.[50] Erythromycin or one of the newer macrolides such as clarithromycin are both effective treatments for mycoplasma pneumonia.[51] Erythromycin reduces the carriage of *U. urealyticum* in the respiratory tract of infants.[64] However, macrolides have not been shown to be effective in preventing the development of chronic lung disease. A large randomized trial is needed.

Chlamydia Trachomatis, Chlamydia Pneumoniae

Chlamydia is an obligate intracellular parasite.

C. trachomatis can cause pneumonia in the newborn. This occurs in around 16 percent of infants of mothers who carry the organism in the birth canal.[52] Infants may present up to 8 weeks of age with cough and tachypnea. Diagnosis relies on culture of nasal secretions or microscopy of conjunctival scrapings, if conjunctivitis co-exists. Treatment is with erythromycin. At follow-up to 8 years, there is a higher prevalence of wheezing in children who had pneumonia due to *C. trachomatis* before 3 months of age.[53]

C. pneumoniae is a common cause of community-acquired pneumonia in school-age children, accounting for 10 percent of cases in one study (31% in secondary school age children).[54] The incubation period is approximately 21 days. Symptoms may initially be upper respiratory, followed by prolonged cough. Treatment is with erythromycin or another macrolide,[50] although the cough may persist for months after treatment. There has been recent interest in a possible role of *C. pneumonie* in the pathogenesis of coronary artery disease. Patients hospitalized with coronary artery disease are more likely to be seropositive for *C. pneumonie* than age-matched controls[55] and *C. pneumoniae* has identified, by PCR, in atheromatous plaques.[56]

SUMMARY

- Viral and 'atypical' organisms are the most common cause of pneumonia in children in the industrialized world. The clinical and radiological appearances may be indistinguishable from bacterial pneumonia. Vulnerable groups of infants or children may have a more severe clinical illness. Where no organism has been isolated and pneumonia has failed to respond to first line antibiotics within 48 hour, empiric therapy with a macrolide will cover many atypical organisms.

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SECTION 2: RECENT ADVANCES IN VIRAL PNEUMONIAS IN CHILDREN

Identyfing the causative organisms of pneumonia in children is challenging, Viruses that typically produce respiratory syndromes are grouped into 5 viral families, one family of DNA viruses and 4 families of RNA viruses (Table 23.1). Over last few years newer viruses have been identified that have been shown to produce significant respiratory problems; these are human metapneumovirus, human parechovirus and newer human coronavirus associated severe acute respiratory syndrome (SARS). However herpes group of viruses, cytomegalovirus (CMV) and measles are also produce life threatening pneumonia especially in immunocompromised children. Pneumonia due to these viruses will not be discussed.

Table 23.1: Viruses producing pneumonia

DNA viruses	RNA viruses
1. Adenovirus (1-51 types)	1. Orthomyxoviridae Influenza A, B and C viruses (Avian Flu-H5N1)
2. Herpes virus	2. Paramyxoviridae Parainfluenza Viruses (1-4 types) Respiratory syncytial viruses (RSV) Metapneumoviruses (hMPV) Measles
3. Cytomegalovirus	3. Picornoviridae Rhinoviruses (1-102 types) Enteroviruses (echovirus 1-34, coxsackievirus A1- A24,B1 –B6) Parechoviruses (1-3 types)
	4. Coronaviridae SARS-CoV.

The infectivity of a particular infectious agent depends on various factors in a given child. Numerous host specific factors such as age, nutritional status, pulmonary defence mechanisms and child's immune response including defects in cellular and humoral immune mechanisms determine vulnerability to a particular viral pathogen. The paediatric population group most susceptible to viral pneumonia are those under 5 years of age. An increased risk of morbidity and mortality from measles pneumonia is seen in younger children with vitamin A deficiency.[1] The spectrum of viral illness in immunocompetent children is different from those with immunosuppression. Apart from the host factors, environmental and physical characteristics of the infective pathogen have an effect on the severity of the illness.

The incidence of viral pneumonia peaks during the winter. Infants born in the late summer are more susceptible as the effect of maternal antibodies decrease. In addition weaning from breast milk, the cold, wet conditions favour the spread of infections such as RSV. Other risk factors contributory to viral pneumonia include underlying lung pathology as in chronic lung disease, gastro-oesophageal reflux, asthma, cystic fibrosis, congenital cardiac disease and immunocompromised conditions. The surface area of an infant's lung is 20 times greater than its body surface area. The exposure to numerous potential infective agents is thus significantly increased with every breath. The physiologic defence mechanisms include muco-cliliary actions of the cells, cough reflexes to clear the airway and immunologic mechanism including secretary IgA, macrophages and other immunoglobulins. Some of these mechanisms that play a vital role in limiting the viral invasion[6] are either immature or poorly developed in infants and small children.

COMMON VIRUSES PRODUCING PNEUMONIA

Orthomyxoviridae

Influenza viruses are enveloped, segmented, ssRNA viruses with a nucleocaspid (NC) surrounding the nuclear material. They are classified into three genre–Influenza A, B, C viruses. The two glycoprotein surface antigen, hem-agglutinin (HA) and neuraminidase (NA) show varied antigenic differences resulting in further classification of Influenza A into 16 HA, 9NA types. All of these subtypes are also identified in birds. Flu A is associated with more severe outcomes than Flu B and C.

In a Finnish study[2] reviewing 936 children over a 23 year period, radiologically confirmed pneumonia was found in 14 percent of patients. Hospitalisation was required in over two-third although the mortality was very low. Secondary bacterial pneumonia due to *Streptococcus pneumoniae* may arise in normal children and this has been shown to be prevented by pneumococcal vaccine.[3]

Paramyxoviridae

Parainfluenza (especially type 3), Human RSV and hMPV are the most important respiratory viruses, which cause epidemics of major medical interest. RSV is the most common cause of lower respiratory tract infection (LRTI) in premature babies and infants. The mechanism of attachment, internalization, amplification of virus along with synthesis of other viral proteins (Ag) and their release from host cell are characteristic for a virus which in turn depends on the antigenic nature and other proteolytic enzymes. This process of invasion, replication, and destruction of airway epithelium initiate host immune response. The duration between inoculation and host response and also the virulence (antigenic strength of the virus) determines the incubation period. All these will result in destruction of viral infected cells and results in breach of respiratory epithelium and increases the risk of super-imposed bacterial infection. These viruses spread by respiratory droplets from cough and contact of an infected person. In childhood community acquired pneumonia, up to 30 percent of children are found to have pneumonia of viral aetiology. Epidemiological studies show that RSV is a commonest pathogen accounting for 14-40 percent of pneumonias, Influenza A and B between 8 percent and 27 percent and parainfluenza between 15-20 percent of all viral pneumonias. Adenovirus is identified in 5-9 percent of pneumonias. Unlike other viruses, Adenoviral pneumonia is less common and not found to be seasonal. Generally it is self limiting infection but however high rates of mortality and morbidity is seen in those infected children and neonates who are immunocompromised.[4]

Clinical Features

In majority of children pneumonia develops either as part of, or shortly after, a viral infection. Viral pneumonia is typically preceded by prodrome of upper respiratory infection namely rhinorrohea, sneezing, nasal blockade, low grade temperature and conjunctivitis. As the disease process progresses, the predominant symptoms may localise anywhere in the respiratory tract resulting in isolated URTI, croup, bronchiolitis or pneumonia. The child will present with various systemic symptoms; lethargy, decreased appetite, malaise, myalgia, headache and high grade fever. This is as a result of an immune response to the ongoing viral invasion mediated through cytokines released from the respiratory tract epithelium rather than the systemic spread of virus. The Incubation period may vary from 1-4 days depending on the viral pathogen. The child then develops progressive lower respiratory symptoms, including fever, tachypnoea, cough and dyspnoea. Chest pain is uncommon unless pleura are involved.

On physical examination (Table 23.2) the child is often febrile, tachypnoeic and tachycardic. As a manifestation of dyspnoea child may show nasal flaring, subcostal, suprasternal and intercostal retractions (chest- In drawing). Grunting is a sign of significant respiratory distress caused by approximation of vocal cords during expiration as an effort to increase the distending pressures for the airspaces. Dehydration and circumoral cyanosis may be observed. Auscultatory findings depend on the stage of pneumonia. Examination of the chest may include crackles, wheeze and areas of decreased air entry. Crackles do not always indicate alveolar disease. However chest findings also depend on the underlying pathology as in asthma, cystic fibrosis and chronic lung disease.

Table 23.2: Signs and symptoms suggestive of Pneumonia

1. Fever
2. Cough
3. Tachypnea
   Infants < 2 months - >60/min
   Infants 2- 12 months - >50/min
   Children >1 year - > 40/min
4. Chest retractions
5. Grunting
6. Cyanosis
7. Auscultation
   Wheeze–Small and large airway narrowing
   Coarse crackles–Secretions/ mucus in the airway
   Fine crackles–Airspace consolidation
8. Chest pain.

Diagnosis

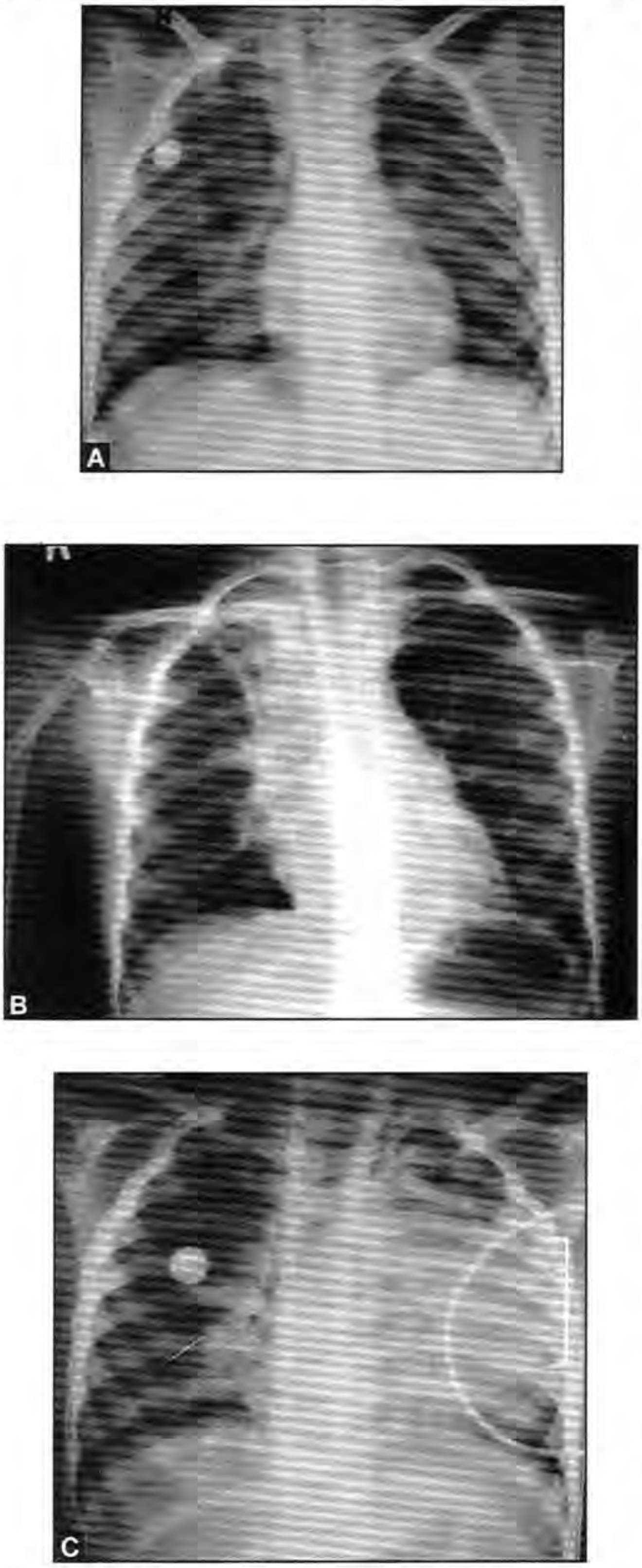
Pneumonia is a clinical diagnosis and should be suspected in any child with cough, tachypnoea especially if is disproportionate to the degree of fever and crackles. Clinical diagnosis of pneumonia of viral aetiology if often challenging due to its varied presentation and is often non-specific. Hence a diagnosis of viral pneumonia should be based on a combination of epidemiological, clinical radiographic and laboratory characteristics.[5-
Various epidemiological features would indicat
pneumonia of viral aetiology. These are occurrenc
during the winter season, age group and children a
high risk with underlying cardiopulmonary o
immunocompromised disease. More than 50 percen
of all pneumonias seen in children less than 3 yea
of age have a viral aetiology.

Radiographic findings in viral pneumonia sho
hyperinflation of the lungs with bilateral interstiti
infiltrates and areas of fine patchy consolidatio
indicating airspace/alveolar disease with streaks
density indicating the presence of both pneumon
and atelectasis.

Figs 23.1A to C X-ray images of various patien
with viral pneumonias and variation in radiologi
findings.

Elevated white blood cells count and increas
number of polymorphonuclear cells and/or ba
forms will increase the likelihood of bacter
infection. In viral pneumonia, there may be a m
elevation of white blood counts with a lymphoc
predominance. In young children with suspec
viral pneumonia, identification of causative organi
is challenging due to the inability to prod
significant sputum or to cough up sputum and p
serological responses especially in infants. Virae
is not very common in the majority of child
Samples aspirated from nasopharynx provi
qualitative specimen in identifying viral aetiol
However, mixed infections with both virus
bacteria account for about 10-40 percent of chil
with pneumonia. Apart from those children

community acquired pneumonia co-infection is a significant factor in severity and is more commonly seen in hospitalized children. Invention of newer laboratory diagnostic techniques has led to the significant progress in identifying viruses in the respiratory tract. However, it is not always true that a virus identified by laboratory testing is the pathogen responsible for the pneumonia. Cytologic evaluation of respiratory secretions, samples obtained from bronchoalveolar lavage and tissue specimens can be examined by using cytologic and histologic methods. While intranuclear inclusions are often seen in cells infected with DNA viruses, cytoplasmic inclusions are usually present in cells infected with RNA viruses. Viral pneumonia can be definitively diagnosed by isolation and identification of the pathogen in viral culture. Proper preservation of specimens for viral culture depends on the use of an appropriate transport medium. Modified cell culture methods, called shell vial culture systems, have been developed to detect viruses rapidly and is quicker time than conventional culture methods.The rapid antigen detection tests (*Immunofluoroscence assay and ELISA*) provide results rapidly and are specific for each virus. Most laboratories use panels of antibodies to common respiratory viruses and hence screen many viruses at once. Usually these will include Influenza, Parainfluenza, RSV and adenoviruses. A newer molecular diagnostic technique for gene amplification, Multiplex reverse transcriptase — (*MRT-PCR*) has been shown to be highly sensitive and specific test. Serological methods demonstrating a raise in antibody titres in both acute and convalescent serum samples will also help to diagnose a recent viral infection. However this test takes longer time to prove a viral etiology in a sick child and is more valuable as an epidemiological tool to define the incidence and prevalence of respiratory viral pathogens.



Figs 23.1A to C: Variation in radiographic findings: Viral pneumonia

Prevention

Hospital infection control measures are aimed at preventing spread of viruses. During seasonal epidemics, high risk infants should be separated from infants with respiratory symptoms. Careful hand washing, use of separate gown and mask should be used in the care of all infants with suspected or established viral infection. Vaccination of infants and

Table 23.3: Anti-viral drugs

Antivirals	Drug dynamics and kinetics	Indications	Side effects
a. Amantidines 1. Rimantadine 2. Amantidine	Inhibits early step in viral replication by preventing internalization and uncoating. Mostly metabolised and excreted in urine. Administered orally as syrup or tablets 5mg/kg.	More effective against Flu A. Less effective against Flu B.	Nausea, vomiting. Amantidine causes anxiety, insomnia and other CNS symptoms.
b. Neurominidase inhibitors. 1. Zanamivir 2. Oseltamivir (tamiflu) 3. Peramivir	Inhibits release of virus and promote clumping thereby preventing spread of virus throughout respiratory tract. Excreted mainly through kindneys. Administered orally as syrup or capsules. Oseltamivir for children > 1 year. 30-75 mg twice daily for 5 days. Zanamivir >7years, 10mg twice daily for 5 days (also as intranasal).	Effective against both Flu A and *B. Paraflu.*	Nausea vomiting abdominal pain. Bronchospasm with zanamivir.
c. Ribavirin	Broad spectrum activity against DNA and RNA viruses. Inhibits viral replication by several mechanisms like inhibiting viral polymerase, inhibition of 5′ cap formation of mRNA and decreases intracellular GTP concentrations. Administered as aerosolised and orally.	Effective against RSV and paraflu. considered in infants and young children at risk of severe RSV disease. IV ribavirin against adenoviral infections.	Highly toxic to bone marrow progeniotors. Anemia, bleeding manifestations.

young children at high risk (chronic lung disease, congenital heart disease, immunocompromised disease, extreme prematurity) during winter season is recommended.[4] The current recommendation is that all children aged between 6 months and 9 years should receive 2 doses of attenuated influenza vaccine if previously unvaccinated. The second dosage should be administered one month after the initial one. The groups of children who should receive vaccination are listed below.

CDC Recommendation: (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm)

1. Children with chronic cardiopulmonary disease
2. Immunocompromised children with diabetes mellitus, renal failure, HIV infection, or other immunosuppressive diseases
3. Patients receiving long-term corticosteroid therapy or other immunosuppressive medications for malignancy.
4. Children receiving long term aspirin therapy who are at risk of developing Reye syndrome following Influenza infection.
5. Health care workers and family members who could transmit influenza to children at high risk.

Immunoprohylaxis: Two immunoprophylactic agents have been approved for prevention of RSV disease. RespiGam is a pooled polyclonal intravenous immunoglobulin preparation enriched in neutralising antibodies against RSV and was recommended against prevention of serious RSV disease in high risk group. It needs large volume infusion and its availability is currently limited. Palivizumab is a monoclonal antibody directed against the RSV fusion glycoprotein. This is 50-100 times more potent than RespiGam and is seen to be effective for prevention of serious RSV infections in children at high risk. Palivizumab is recommended during RSV season as monthly intramuscular injection for premature babies (<32 wks of gestation) and children in high risk group. Some studies have shown a reduction of 45 percent of hospitalization in the treated group.

Chemoprophylaxis

Table 23.3 outlines current treatments available for viral pneumonias. Both amantidine and rimantidine are effective in prevention of Influenza A infection. It is recommended that everyone in an institution, including unvaccinated staff should be treated for at least 2 weeks during the out beak or up to 1 week after the end of the outbreak regardless of prior vaccination against influenza. Neurominidase inhibitors are also found to be very effective.

Vaccination against RSV, Parainfluenza and metapneumovirus have been unsuccessful.

Treatment

If the viral etiology is strongly suggested in a child with pneumonia, it is advisable to withhold antibiotic therapy. However up to 40 percent of children with viral pneumonia may have co-infection with bacteria and hence any deterioration in clinical condition should alert the paediatrician to reconsider antibiotic administration. Along with general supportive measure in children who are mildly ill, more advanced management including ventilator support is considered in severely ill children. Although there are various antiviral drugs against different viral pathogens, they seem to be effective in reducing the duration of assisted ventilation but no significant impact on mortality rates, length of hospitalisation and pulmonary functions have been demonstrated. Dexamethasone has been used in the treatment of RSV and other viral pneumonia. Although it does not alter the clinical outcome it is often used in infants with underlying chronic lung disease and who are difficult to wean off the ventilator following pneumonia. But again the evidence of efficacy is very unsatisfying. Alpha Interferons are glycoprotiens that induce antiviral, antiproliferative and immunological effects in patients with viral infection. They have been used in picornovirus infections (rhinovirus, parechovirus) as intramuscular or subcutaneous injections although the evidence is lacking for regular use.

Prognosis and Complications

Generally prognosis for recovery is good although freedom from cough usually takes few days to weeks. Some children continue to shed virus for longer time especially those who are immunocompromised. Viral pneumonia could be life threatening in children at high risk. Neonates and young children at high risk will have fatal outcome with adenoviral pneumonia and survivors may have residual airway damage with bronchiolitis obliterans, bronchiectasis or rarely interstitial fibrosis.

Note

a) Current avian flu H5N1 virus (Z Strain) is resistant to Amantidine but the neuramnidase inhibitors are found to be effective. b) There are many other antiviral agents under consideration against different viruses but they all need bigger clinical trails.[3]

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CHAPTER

Persistent and Recurrent Pneumonias

Praveen Khilnan

Recurrent chest infections are a common reason for children to be seen by their general practitioner (GP) or a pediatrician. Recurrent or persistent cough may be the only symptom, but often there is also a history of wheeze, breathlessness, sputum production or general ill health. A number of disorders can present with these features (Table 24.1). Many of these children are simply having the repeated viral upper respiratory tract infections that are a normal part of growing up. In others, the symptoms are the first manifestations of asthma. But, in an important minority there is a clear history of persistent or recurrent episodes of pneumonia, or of chronic sputum production, indicating more severe pathology.[1]

Table 24.1: Causes of recurrent or persistent cough

Asthma	Very common
Recurrent 'normal' infections	Very common
Prolonged infection (e.g. pertussis, mycoplasma, RSV)	Common
Cigarette smoking (passive/active)	Common
Habit or psychogenic cough	Common
Idiopathic	Common
Aspiration	Uncommon
Gastro-esophageal reflux	Uncommon
Incoordinate swallowing	Uncommon
Intrabronchial foreign body	Uncommon
Mediastinal or pulmonary tumors	Very rare
Suppurative lung disease	All uncommon
Cystic fibrosis	
Post-infective (e.g. adenovirus, pertussis)	
Tuberculosis	
Ciliary abnormalities	
Congenital abnormalities of the respiratory tract	
Retained foreign body	
Immunodeficiency	

The challenge for the clinician is to distinguish between the child with self-limiting or minor problems and the child with serious, perhaps progressive, lung disease.

It is necessary to assess the severity and to diagnose the cause of the symptoms. This depends very much on taking a detailed history, on detecting any abnormal physical -signs, and in selected cases, on the use of appropriate investigations. There needs to be a high index of suspicion about uncommon disorders, such as immunodeficiencies, ciliary abnormalities, or congenital anomalies of the respiratory tract.

When assessing children who present with repeated chest infections, it is important to recognize the factors that affect the incidence of these infections in children (Table 24.2).

Table 24.2: Risk factors for lower respiratory infections in children

- Age
- Male sex
- Prematurity
- Parental smoking
- Large family size, overcrowding
- Congenital abnormalities
- Immunodeficiency

The child's age influences the type and frequency of all respiratory infections. The normal fall in the incidence of lower respiratory tract infections (LRTis) with age reflects the pattern of exposure to infection and the development of the child's immunity. Some infections occur only in children within a specific age group. For example, acute bronchiolitis occurs almost exclusively in infants aged 1-8 months, although many affected children have recurrent cough, wheeze and breathlessness for months or years afterwards. Age also affects severity and two-thirds of childhood deaths due to respiratory infections occur in infancy. Lower respiratory infections are more common in boys than girls, for reasons that are not understood.

Infants born prematurely, and particularly those who develop bronchopulmonary dysplasia (chronic lung disease of prematurity) after ventilation, frequently require hospital admission for respiratory infections in early childhood. The mortality from infection in these infants is higher than in term infants.

The immuno-protective effect of breast feeding against respiratory infections is most important in non-industrialized countries, but is also evident in industrialized societies.[2]

Parental smoking increases the risk of all respiratory illnesses and symptoms, and particularly lower respiratory tract infection, in children. The effect is greater in infants than in older children, is related more to maternal than paternal smoking, and is dose-related. Both maternal smoking during pregnancy and postnatal passive exposure predispose the children of smokers to recurrent respiratory infections and symptoms.[3]

Exposure to other children influences the number of infections children develop. Infants with older siblings or from over-crowded homes, have more frequent respiratory infections. When children first attend school or nursery, the number of infections they contract rises.

Children with congenital defects of the respiratory tract, such as tracheoesophageal fistula or sequestration, and children with congenital heart disease, are at increased risk of recurrent respiratory infection. Neurologically handicapped children are particularly vulnerable. Recurrent or persistent chest infections are a common presenting feature of cystic fibrosis, the commonest cause of bronchiectasis in children. Infections in all of these groups of children are not only more common but also more severe than in normal children, with a greater risk of respiratory failure and death.

Table 24.3: Lung defense mechanisms

Physical and physiological defenses
- Airway filtration of particles
- Cough
- Sneezing
- Bronchoconstriction
- Mucociliary clearance
  - Airway mucus
  - Respiratory cilia
- Alveolar fluid movement

Cellular defenses
- Lymphocytes (T- and B-cells)
- Pulmonary macrophages
- Neutrophils

Secretory defenses

Immunoglobulins G, A, M and E
Collectins
Alfa 1 Antitrypsin and alfa 2-macroglobulin
Complement
Alfa and beta Defensins
Lactoferrin
Lysozyme
Interferon

Some children with recurrent or persistent chest infections have a defect in the complex system of defense mechanisms which normally protect the lungs from a hostile microbiological environment. These include physical defenses such as cough and mucociliary clearance, circulating and resident cellular defenses, and a range of humoral or secretary mechanisms (Table 24.3).

Differential Diagnosis of Recurrent Chest Infections

Most children referred with recurrent respiratory infections have normal immune and other respiratory defenses. They are simply at one end of the normal distribution of acute respiratory infections, often because of their age or environment. Characteristically, they are growing and developing normally, the examination and chest X-ray are normal between episodes, there is no family history of severe infections, and no serious extrapulmonary infections. Reassurance is all that is required.

Asthma

Despite recent advances in care, many children referred with 'recurrent chest infections' or a 'persistent cough' will be shown to have undiagnosed asthma.

Closer attention to the history reveals that most, but not all, have recurrent episodes of cough, wheeze and breathlessness, often with the characteristic trigger factors of upper respiratory tract infections (URTIS), exercise, cold air, emotional upset, or exposure to pets and other aero-allergens.

There is often a personal or family history of other atopic conditions such as eczema or allergic rhinitis. They may have responded to bronchodilators or anti-inflammatory therapy. Examination is often normal at the time of consultation, but spirometry may indicate airways narrowing and bronchodilator responsiveness. In some children, asthma co-exists with another disorder, such as a specific antibody deficiency. Signs which suggest an alternative or additional diagnosis include asymmetric or focal chest signs, finger clubbing, failure to thrive or the features of systemic disease. A cough productive of purulent sputum is not a feature of asthma.

Post-infective Cough

Some parents clearly describe a cough which first appeared with an acute infection and which has persisted for weeks or months since. This is common after Bordetella pertussis (whooping cough) and *M. pneumoniae* infections.[4] With these pathogens the cough, which may be paroxysmal, may yield clear or white mucus. It is the result of the bronchial hyper-reactivity and impaired mucociliary clearance that follow the inflammation that occurs with these infections. The cough normally subsides within 2-6 months. Episodes of wheeze, cough and breathlessness, which may recur for months or years, are common in infants who have been admitted to hospital with RSV bronchiolitis.[5,6] The pathophysiology of this 'post-bronchiolitis syndrome' is complex, involving abnormalities of both immune function and airway growth.

Inhaled Foreign Body[7]

The possibility of an inhaled foreign body should be considered in any young child who develops a persistent productive cough, particularly if there has been an acute onset after an episode of choking. Some intrabronchial foreign bodies, notably peanuts, evoke severe inflammation of the bronchial mucosa which quickly leads to airways obstruction and distal infection. Even after the diagnosis of a foreign body has been made and it has been removed bronchoscopically, there may be persistent localized airway damage, abnormal lung function and a persistent cough.

Chronic Suppurative Lung Disease

In a minority of children who present with recurrent chest infections, the cardinal symptom is a persistent or recurrent loose cough that is productive of yellow or green sputum. This suggests chronic suppurative lung disease (see Table 24.1) and possibly bronchiectasis, which is defined as cylindrical or saccular dilatation of the subsegmental bronchii. The incidence of these conditions is unknown.[8] Some children with chronic suppurative lung disease present with recurrent or persistent pneumonia: while any normal child can have one episode of pneumonia, recurrent or poorly resolving episodes often indicate an underlying abnormality.

Some of these children will also have recurrent ear or sinus infections. Wheeze and chest pain are present in over a fifth of children with bronchiectasis.[8]

As the differential diagnosis includes several inherited conditions (for example, cystic fibrosis, ciliary dyskinesia and some immunodeficiencies), it is important to take a detailed family history of severe or recurrent respiratory or systemic infections in childhood. As certain acute infections, such as adenoviral pneumonia, can lead to bronchiectasis, it is vital to obtain a detailed history of the first episode of symptoms. A history of swallowing difficulties or choking with feeds, or of gastro-esophageal reflux, should be sought as recurrent aspiration of feeds is an important cause of recurrent pneumonia[1] and chronic suppurative lung disease, particularly in children with neurodevelopmental problems.[9,10] The acute onset of symptoms after an episode of choking is highly suggestive of an inhaled foreign body in young children.

The clinical examination may reveal important signs such as wheeze, crackles, hyperinflation, finger clubbing, hepatosplenomegaly, nasal disease, skin lesions and failure to thrive. A plain chest X-ray may show either focal or widespread changes such as atelectasis, hyperinflation, consolidation or abnormal patterns of the airways. The left lower, lingula and right middle lobes are most commonly affected.

Cystic Fibrosis

(See Chapter on Cystic Fibrosis)

Cystic fibrosis is the commonest cause of chronic sup-purative lung disease in children, affecting one in 2500 births in Caucasians. Most affected children present with recurrent chest infections in early childhood and over 90 percent also have malabsorption and failure to thrive due to pancreatic insufficiency. About 10-20 percent present with neonatal intestinal obstruction due to meconium ileus. Others are diagnosed because of a family history of this autosomal recessive condition or by neonatal screening. Viscid mucus in the small airways predisposes to chronic infection, initially with *Staphylococcus aureus* or *H. influenzae*, but later with *Pseudomonas aeruginosa*. The infection, and the inflammatory response to it, lead to progressive damage of the bronchial wall, bronchiectasis, cystic lesions and eventually lung fibrosis. Cystic fibrosis must always be considered early in the differential diagnosis of recurrent chest infections.

Bronchiectasis Following Acute Pneumonia

In the past, many cases of childhood bronchiectasis followed acute lower respiratory tract infections with pertussis, measles or tuberculosis. This is now rare. Virtually all children with normal immune function will make a full recovery from pneumonia or bronchiolitis, even if the acute episode was severe. However, there are important exceptions to this rule. Adenovirus serotypes 3, 4, 7, and 21 can all cause severe bronchiolitis, pneumonia and death.[11,12] Up to 40-70 percent of survivors are left with permanent damage to the airways (bronchiolitis obliterans) with segmental or lobar atelectasis, areas of hyperinflation and impaired lung function.[13] A quarter of children with bronchiolitis obliterans subsequently develop bronchiectasis.[14] Typically, these children are left with persistent wheeze (which responds poorly to bronchodilators), a persistent cough (which is initially dry but then becomes productive of purulent sputum), and the characteristic radiological changes of bronchiolitis obliterans. Swyer-james or MacLoed's syndrome, where there is a small hyperlucent lobe with impaired perfusion and ventilation, has also been described after these infections. Similar damage can follow severe mycoplasmal pneumonia. Co-infection with both adenovirus and *M. pneumoniae* is particularly devastating.

Although most children make a full recovery from bacterial pneumonia, in some there is slow or incomplete resolution, with persisting localized clinical signs and atelectasis or inflammation on the chest X-ray. This may be due to obstruction of a bronchus by a plug of muco pus or localized damage to the bronchus and the adjacent lung parenchyma, but in some cases it reflects an underlying abnormality of the lung anatomy or defenses or an inhaled foreign body. The cough continues and may become productive of sputum, there may be exacerbations with fever. These children need detailed assessment.

Immunodeficiency Disorders

(See Chapter on Immunodeficiency)

The respiratory tract is the organ system most commonly involved in immunodeficiency disorders. There is often a delay of years between the onset of symptoms and the diagnosis being made. This delay increases the risk of bronchiectasis and irreversible lung damage occurring before appropriate treatment is given.[15]

An immune defect should be considered in any child who has respiratory infections that are unusually severe, recurrent, unresponsive to conventional treatment, or atypical.

Common associated features include failure to thrive, which is often secondary to gastrointestinal disease, severe atopic disease such as eczema, and occasionally, auto-immune disease.[15,16]

Some children with certain syndromes, such as DiGeorge and Down's syndromes, have abnormalities of their immunity as well as cardiac, facial and other anomalies. As many immunodeficiencies are inherited, a family history of severe infection or early death or consanguinity should be sought. As well as respiratory infections, there may be severe infections of the skin, gastrointestinal tract and soft tissues, and lymphadenopathy. The clinical

Table 24.4: Classification of primary immunodeficiencies

Immunodeficiency	Major pathogens
Antibody (B-cell) deficiency	
X-linked agammaglobulinemia (XLA)	*H. influenzae*
IgA, IgG subclass deficiency	*Strep. pneumoniae*
Specific antibody deficiency	Giardia lamblia
Common variable immunodeficiency	ECHO virus
	Salmonella spp.
	M. Pneumoniae
Defective cellular immunity (T-cell deficiency) and severe combined immunodeficiencies (SCID)	
Adenosine deaminase (ADA) deficiency	Herpes simplex, zoster
Hyper IgM syndrome	CMV, EBV, Measles, RSV
Major histocompatibility complex deficiency	*Pneumocystis. carinii*
Wiskott-Aldrich syndrome	*Streptococci, H. influenzae*
	Candida, Aspergillus
	Mycobacteria (typical and atypical)
	Cryptosporidium
Phagocyte defects	
Chronic granulomatous disease (CGD)	
Familial, cyclical or auto-immune neutropenia	
Leukocyte adhesion defects	
Hyper IgE syndrome (Job's syndrome)	
Complement deficiency	*Staph. aureus*
Mannose-binding protein	*Streptococci*
C3 or C5 deficiency	Candida, Aspergillus
	Enteric Gram-negative bacteria

examination is often abnormal in children with immunodeficiency.

Immunodeficiencies are classified as *primary* (congenital) or *secondary* (acquired) (Table 24.4).

In the past, secondary immunodeficiencies were most often the result of disorders such as malignancy, immuno-suppressive therapy, measles, or malnutrition, but in many countries HIV infection is now the commonest cause of acquired immunodeficiency.

Over 80 different primary immunodeficiencies have been identified. These can be classified on the basis of which of the four sections of 'the immune orchestra' (antibodies, T-lymphocytes, phagocytes or the complement system) is involved, but disorders in which there are abnormalities in more than one section are common.

For example, in the severe combined immunodeficiencies (SCID), which are the most severe disorders, there are defects in both cell-mediated (T-lymphocyte) and antibody (B-lymphocyte) function. Defects of humoral (antibody) immunity account for 50 percent of primary immunodeficiencies, combined humoral and cellular deficiencie constitute 20-30 percent of cases, phagocyte defect approximately 18 percent and complement defect less than 2 percent.[15]

As one would expect, the younger the child whe infections first appear, the more severe the immun defect is likely to be. Most defects involving cel mediated immunity present within the first 6 month of life, frequently with the triad of pneumonia intractable diarrhea and mucocutaneou candidiasis.[15] Antibody deficiencies such as X-linke agamma-globulinemia (XLA), often cause recurren respiratory infections between the ages of months—when levels of maternally derived Ig have fallen—and 2 years of age, but there is often delay of 2-5 years before the diagnosis is made.[1] Phagocyte and the rare complement defects can als present at this stage. Common variable immuno deficiency, a heterogeneous group of disorders wit hypogammaglobulinemia and defective antibod production, usually presents after the age of 5 year often in the second or third decade of life.

Table 24.4 lists the major categories of immunodeficiency and gives some examples of disorders within each category that can present with severe, recurrent, persistent or unusual chest infections. As the nature of the immune defect determines the susceptibility to particular microorganisms, identifying the pathogen is not only important in deciding what treatment is appropriate, but it may also indicate which part of the immune system is defective. For example, identification of Pneumocystis carinii and cytomegalo virus (CMV) in bronchial lavage fluid from a child with interstitial pneumonia would suggest a defect of T-cell function, whilst recurrent cavitating staphylococcal pneumonia, which is refractory to appropriate antibiotics suggests a neutrophil defect, such as chronic granulomatous disease.

Defects of Antibody Production

Antibody deficiencies are the commonest of immuno-deficiencies. There are many different types of antibody deficiency, ranging from severe deficiencies of all immunoglobulins (X-linked agammaglobulinaemia, Bruton's disease) to milder deficiencies of specific antibodies in children with normal immunoglobulin levels.

The normal term infant has undetectable serum levels of IgM and IgA at birth and these rise progressively in the first 2-3 years of life.[16,17] The maternal IgG which crosses the placenta into the fetus disappears within 5-7 months. The infant's own IgG appears at significant levels at 4-8 months and rises for 2-3 years. Anti-protein antibodies are produced in the first few months of life, but the ability to produce IgG antibodies against polysaccharide antigens, such as the capsules of certain bacteria, matures much more slowly and is only effective after 2 years. IgG has four subclasses (1-4) which differ in concentration, structure and function. Antibodies against protein are mainly of the IgGl and IgG3 subclasses and those against polysaccharides are predominantly of the IgG2 subclass.

It is now recognized that many children with recurrent chest infections have abnormalities in their ability to produce specific antibodies to common respiratory pathogens such as the *Strep. pneumoniae* or *H. influenzae* which is commonly isolated from their sputum. Many of these children are diagnosed as suffering from asthma and are receiving high doses of inhaled steroids and other asthma therapies. Important clues to the diagnosis include the lack of response to high doses of asthma treatment, the presence of a productive cough and colored sputum, and improvement with courses of antibiotics. There may be a history of recurrent upper respiratory infections, such as otitis media or tonsillitis. If an antibody deficiency is suspected, total serum levels of IgG, IgM, IgA and IgE should be measured.

Investigations

Antibody deficiency Immunoglobulins (G, A, M), IgG subclasses, specific antibodies, B-cell populations.

Defective cellular immunity White cell differential, Chest X-ray (thymic shadow) Lymphocyte populations, Mitogen responses.

Phagocyte defects White cell differential, Chemotaxis, phagocytosis Nitroblue tetrazolium test.

Complement deficiency C3, C4, CH 50 levels.

As the normal ranges of these proteins change during childhood, the measured values must be compared to the age appropriate normal values, ideally from the same laboratory. There is controversy also about the value of measuring IgG sub-class levels, as not all children with 'deficient' sub-classes have evidence of an increased susceptibility to infection.[18] Nevertheless, IgG subclass deficiency, and particularly IgG2 deficiency, can be associated with severe bronchiectasis and many clinicians still measure IgG subclasses.

It is important to measure serum levels of specific antibodies against protein antigens (tetanus and diphtheria toxoids) and polysaccharide antigens (H. *influenzae type b [Hib] and Strep. pneumoniae).* A key element of the evaluation of humoral immunity is the assessment of the child's ability to produce normal levels of specific antibodies in response to the routine childhood immunizations or 4 weeks after test vaccinations with Hib and polyvalent pneumococcal vaccines (Pneumovax). Care is needed in the interpretation of these tests as the child's age profoundly influences the response to these immunizations. For example, a persistently low level of anti-pneumococcal antibodies after Pneumovax in a 10-year-old suggests a pathological defect in antibody production, whereas low levels and the lack of a response in a 2-3-year-old is normal and simply indicate physiological immaturity. It is difficult to make a definite diagnosis of a specific anti-pneumococcal antibody deficiency in a child aged less than 5-6 years.

Selective IgA deficiency is the commonest immunodeficiency with an incidence of 1:400-700.[16,17] Many affected individuals are asymptomatic, but others, and particularly those who have an associated IgG subclass or specific antibody deficiency, suffer from recurrent sino pulmonary infections. As serum IgA levels are low in healthy children and do not reach adult levels until the age of 8 or 9 years, a diagnosis of IgA deficiency should not be made in children below the age of 4 year.[17]

In another important antibody deficiency, X-linked agammaglobulinemia, there are low or undetectable levels of all the major immunoglobulins due to abnormalities of the BTK gene and B-cell differentiation in affected boys. There may be an associated neutropenia. Pyogenic infections such as pneumonia first appear after 6-12 months. Unless treated with regular intravenous or subcutaneous immunoglobulin therapy and aggressive antibiotic treatment of acute infections, this progresses rapidly to chronic bacterial bronchitis and irreversible lung damage with bronchiectasis.

T-cell Deficiencies

T-lymphocytes are essential not only in controlling viral, fungal, mycobacterial and protozoal infections, but also in aiding B-cells to produce immunoglobulins.[17] Children with T-cell deficiencies can present with severe bacterial infections as well as the classic opportunistic infections. Primary T-cell deficiencies are rare inherited disorders. Children with severe combined immunodeficiency (SCID) have profoundly defective T-cell and B-cell function. Although they can present with recurrent chest infections, these are often associated with other severe acute infections, including septicemia, severe and refractory mucocutaneous fungal infections and enteropathies.[19] Most untreated children die in infancy and the only cure is bone marrow or stem-cell transplantation.

Many children with DiGeorge syndrome, in which there is a microdeletion of chromosome 22q11.2, have a milder T-cell deficiency, with reduced lymphocyte and T-cell numbers and poor *in vitro* T-cell proliferation responses to mitogens such as phyto hemagluttinin or poke weed mitogen. These defects often improve as the child grows older, but affected children may have recurrent chest infections and bronchiectasis in early childhood.

Phagocyte Disorders

Primary disorders of phagocyte numbers or function are relatively uncommon in children.[20] Recurrent sinopulmonary, gastrointestinal and soft tissue infections due to *Staph. aureus, Burkholderia cepacia, Serratia marcascens* and fungi are the usual mode of presentation. In boys with chronic granulomatous disease (CGD), the commonest serious phagocytic disorder, in which there is defective killing of ingested micro-organisms, cavitating pneumonia which responds poorly to antibiotic therapy is a common presentation. Severe pneumonias, empyemas and bronchiectasis are common in children with the hyper-IgE (Job) syndrome, who have a wide variety of defects of neutrophil, lymphocyte and humoral function as well as very high levels of serum IgE.[21]

Disorders of Ciliary Function

In healthy children, the microcilia of the respiratory epithelium beat in a regular coordinated manner, propelling mucus proximally to the oropharynx where it is swallowed or expectorated. The mucus provides both a physical and a chemical barrier to pathogens.

The estimated prevalence of primary ciliary dyskinesia (PCD) is 1:16,000-20,000. Recent developments in high speed digital imaging have led to the identification of an increasing number of congenital defects of ciliary structure, beat pattern and frequency when used in conjunction with electron microscopy studies of nasal epithelial brush biopsies. Many cases of PCD are undiagnosed[22] reflecting poor awareness of the spectrum of the clinical patterns of these disorders and the difficulty in making an accurate diagnosis. Most cases are autosomal recessive, but other patterns of inheritance have been reported—the affected genes have not yet been identified. Males and females are equally affected. Children with primary ciliary dyskinesia have abnormal mucociliary clearance. PCD may present in newborn infants with tachypnea or pneumonia, sometimes associated with nasal obstruction and a mucopurulent discharge. In the older infant and child, it typically presents with a persistent productive cough, atypical asthma, or occasionally severe gastro-esophageal reflux, and later with the features of bronchiectasis. As the upper respiratory tract is also affected, chronic purulent rhinitis, sinusitis, and chronic secretary otitis media with effusion and conductive deafness are often also present. Half of children with classical Kartagener's syndrome have situs inversus and dextrocardia in addition to these features and there is an increased incidence of congenital heart disease, hydrocephalus and esophageal atresia. Most affected males are infertile because of immotile spermatozoa and affected women can be subfertile.

Making the diagnosis of primary ciliary dyskinesia is technically difficult. It depends on the assessment on ciliary structure and function using the specialized techniques mentioned above and few centers have the ability to produce reliable results. False negatives and false positives do occur. Abnormal ciliary function is also seen in asthma, cystic fibrosis and after certain viral and bacterial infections (secondary ciliary dyskinesia). Traditional tests of mucocillary clearance, such as the saccharin test, are not reliable in children. Nasal nitric oxide is lower in children with PCD than in healthy controls or children with asthma and other forms of bronchiectasis and this may prove to be a useful screening test for this group of conditions in the future.[23]

Congenital Abnormalities of the Lung

(See Chapter 31 on Congenital Abnormalities of the Lung)

Recurrent or persistent chest infections are common in children with congenital abnormalities of the airways, lung parenchyma and pulmonary vasculature.[23,24] For example, repeated episodes of pneumonea are often the presenting feature of lobar sequestration, bronchial stenosis and broncho malacia, and cystic adenomatoid malformations of the lung.[25] Such an abnormality should be suspected if one lobe is repeatedly infected or if there is incomplete resolution after treatment. Computerized tomography and magnetic resonance scanning are helpful in defining the anomaly prior to surgical excision. Children born with esophageal atresia and tracheo-esophageal fistula often have repeated episodes of pneumonia and bronchitis in early life as a result of persisting abnormalities of airway and esophageal function.[24] The condition has an incidence of 1:3000 and associated vertebral, anal, cardiac, renal or limb defects (VACTERL anomalies) are seen in up to 50 percent of affected children.[25] In one series of 334 survivors of tracheo-esophageal fistula with esophageal atresia, 31 percent had one or more episodes of pneumonia in the first 5 years of life and 5 percent had been admitted on more than 5 occasions. Many more had recurrent 'bronchitis' in childhood.[26] The rates of pneumonia and bronchitis fall as the children grow older. Gastroesophageal reflux, esophageal dysmotility and strictures all predispose to recurrent aspiration pneumonia in these children. Some require further esophageal surgery to prevent progressive lung damage and to allow adequate nutrition. Both restrictive and obstructive patterns of lung dysfunction are present in 18-60 percent of survivors.[27,28]

Tuberculosis

Tuberculosis should be considered in any child with a persistent productive cough, particularly if there are systemic features such as fever, weight loss or general malaise. Since most tuberculous infections are transmitted by inhalation, primary lesions occur in the lungs in over 95 percent of infected children. As with adults, there are several different clinical and radiological patterns of lung disease that can develop from the primary complex. These include effusions, cavitation, bronchial obstruction due to mediastinal lymphadenopathy with atelectasis or distal emphysema, tuberculous pneumonia, endobronchial tuberculosis, or miliary disease. Post-tuberculous bronchiectasis is rare nowadays. Extrapulmonary manifestations, of which meningitis is the most serious, are more common in children than in adults. The diagnosis depends on a high index of suspicion, tuberculin skin testing, radiology, and microbiology of sputum and gastric washings.

Investigation of the Child with Chronic Suppurative Lung Disease

It is impossible to overemphasize the importance of the clinical history and examination in the assessment of these children. The plain chest X-ray is valuable in assessing the severity and distribution of lung involvement. Wide-spread changes such as bronchial wall thickening or inflammation involving several lobes suggests a systemic disorder such as cystic fibrosis, ciliary dyskinesia or an immunodeficiency disorder. Focal changes are more common if there is a congenital abnormality, an inhaled foreign body or bronchial obstruction for some other reason. *High resolution computerized tomography (HRCT) is more sensitive than plain radiographs at revealing bronchiectasis, it has largely replaced bronchography.* It can also show localized areas of gas-trapping (hyperinflation) and interstitial fibrosis not evident on the chest X-ray, for example in children with bronchiolitis obliterans. CT scanning and magnetic resonance imaging are both helpful for assessing congenital anatomical abnormalities, such as seque-stration or cystic adenomatoid malformations. Isotope scans provide useful evidence about regional ventilation and perfusion.

All children with persistent cough should have their sweat electrolytes measured. The sweat test remains the standard diagnostic test (> 60 mg/dl) for CF, although CF gene mutation studies are being used increasingly. Other investigations include bacteriological studies on sputum if this can be produced; viral and mycoplasmal antibody levels; tuberculin skin testing; and in selected cases, immune function tests. All children should get a full blood count and white cell differential, persistent lymphopenia or neutropenia may be present even when the child is well.

Which immune tests are performed will depend on the nature and severity of the respiratory symptoms. For example, in the child who has repeated episodes of cough with purulent sputum containing Strep. pneumoniae or H. influenzae, but who is otherwise well with no clinical or radiological evidence of lung damage, *measurement of immunoglobulin and immunoglobulin subclass levels,* and specific antibody levels against pneumococcus, tetanus and Hib would be appropriate, as a specific antibody deficiency is the most likely diagnosis. Children with low Hib and anti-pneumococcal antibody levels should be immunized with Hib vaccine and (over the age of 4 years) Pneumovax and have their antibody levels repeated 4-6 weeks later. By contrast, a child with severe opportunistic pneumonia demands a detailed assessment of cellular and humoral immune function (see Table 24.4). This should be planned with a clinical immunologist.

Flexible fiberoptic bronchoscopy is now established as a key investigation in the assessment of children with chronic lung sepsis or suspected immunodeficiency. Microbiological and cellular specimens can be obtained by suction, by the use of a protected brush, or by bronchoalveolar lavage. Bronchoscopy also allows a detailed evaluation of the tracheobronchial anatomy and dynamics and identification of unsuspected foreign bodies. If recurrent aspiration is suggested by the history, this may be detected by isotope milk scans. Incoordinate swallowing, which is most commonly seen in children with severe neurodevelopmental problems such as cerebral palsy or severe myopathies, should be assessed by video fluoroscopic barium swallow.[26] Although esophageal pH monitoring can give both false positive and false negative results, it remains the best test for assessing the frequency and severity of gastro-esophageal reflux. Respiratory ciliary studies require referral to a specialist center.

SUMMARY

There are many different causes of recurrent chest infections in children. The clinician has to distinguish between children with self-limiting or easily managed conditions, such as recurrent acute viral infections or asthma and those with more severe, often progressive, diseases. It is important to understand the epidemiology of acute respiratory infections in children and also the factors that influence the pattern of these common infections.

A chronic or recurrent cough productive of purulent sputum, or repeated episodes of pneumonia, suggest chronic suppurative lung disease and the possibility of bronchiectasis. These children require detailed and specialist assessment.

The commonest causes of suppurative lung disease are cystic fibrosis, immune deficiencies, congenital lung and ciliary abnormalities, and lung damage caused by acute pneumonia. Other causes include an unsuspected foreign body or recurrent aspiration.

Although a meticulous history and examination are vital in assessing these children, specialist investigations including sweat tests, immune and ciliary function tests, and bronchoscopy are often indicated. Plain radiology, CT and MR scanning can all help define the site and severity of any abnormalities such as bronchiectasis, atelectasis or congenital anomalies. A multidisciplinary team approach to the assessment and care of this demanding and complex group of children is essential.

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CHAPTER

25

Recent Advances in the Rapid Diagnosis of Respiratory Tract Infection

Praveen Khilnani

Molecular techniques have enabled major advances in the speed and sensitivity of the laboratory diagnosis of respiratory infections. This has, in general, made the diagnosis of respiratory tract virus infection more reliable and speedier.

This chapter does not intend to be a comprehensive treatise on the rapid diagnosis of respiratory infections. There are several excellent textbooks that cover the field in detail.[1,2] It will, instead, focus on recent and future trends.

Molecular Probes

Molecular probes have the advantages over conventional culture methods of greater speed, specificity and sensitivity. Apart from detection, molecular methods are now becoming standard technologies for establishing quantitative estimates, particularly with regard to monitoring treatment, and resistance to therapy.

Detection of Virus

Almost all human viruses have had probe methods described for their detection. Polymerase chain reaction (PCR) has had wide-spread applicability to the detection of viruses in a range of specimen types. For DNA viruses; this is straightforward, for RNA viruses; an additional reverse transcription step is required either by a separate reverse transcriptase (RT) enzyme or a DNA polymerase, such as Thermus thermophilus DNA polymerase, which has RT activity. With respiratory specimens, which may have a number of different viruses or even mixed infec-tions multiplex PCR methods have been developed. This involves using probes to several different viruses in a single amplification reaction. Another use of multiplex PCR is to type viruses, such as parainfluenza viruses.

Although PCR methods have been the most commonly used, other nucleic acid amplification technologies have also been applied to viruses. Target amplification systems, which produce multiple copies of the target nucleic acid rather than the probe, such as self-sustained sequence replication (3SR) have been used to amplify viral genes. Ligase chain reaction (LCR) is useful for the detection of mutations. If two primer probes bind contiguously to the target DNA, they can then be amplified by repeated hybridisation/disassociation cycles.

Qbeta replicase amplification appears to be less sensitive than PCR because of high background amplification of unhybridized probe recombinant. Its advantages are that it can detect both RNA and DNA targets and is more easily quantifiable than PCR.

Quantitative Viral Estimation

PCR, nucleic acid sequence-based amplification (NASBA) and branched chain DNA (bDNA) amplification methods have all been applied to quantification of viral load in the clinical setting.

Quantitative competitive PCR includes a target sequence mimic (imitator) which contains a template (control sequence) which is amplified as efficiently as the actual target.Viral load is then compared to the control load.

Detection of Novel Agents of Disease

Novel respiratory viruses continue to be identified. The identification of such viral pathogens has been achieved by subtractive technologies, allied to amplification methods. Representational differential analysis (RDA) simultaneously combines amplification and subtraction. After restriction enzyme digestion to reduce genome complexity, linkers are added to the products to enable subsequent PCR amplification. As with other probe methods, *in situ* PCR is becoming the advancement of choice. Indirect methods involve adding standard PCR reagents to the fixed cells and then post-amplification the products are detected by standard *in situ* hybridization.

Bacteria Identification

Bacteria have a circular DNA genome that represents its chromosome. Methods have been developed which facilitate the detection of chromosomal, plasmid or total DNA in a wide range of bacteria. In addition, the advent of methods such as PCR has enabled the detection of previously undiscovered pathogens.

Traditional methods of diagnosis, as with other bacterial pathogens, have relied on microscopy and culture. Neither method is, however, as rapid as PCR-based methods. Zeihl Neelson (ZN) stain and culture continue to be used for diagnosis of mycobacterial infections although time consuming. In one study[3] Eisenach *et al* examined 162 sputa for presence of IS6110 genes. All those that were Zeihl Neelson (ZN) smear positive were also PCR positive. One of two smear-negative, culture-positive samples were PCR-positive. Two of the 43 smear-negative, culture-negative specimens were also PCR-positive. 26 non-mycobacterial specimens were PCR-negative and one of 42 non-tuberculous mycobacterial specimens was negative. Other studies[4] have supported that PCR is more sensitive than ZN stains. Although culture still appears to be more sensitive than single-round PCR, advances such as multiple primer and nested methods improve sensitivity.

Apart from PCR, the literature describes other amplification methods for the detection of bacteria. The diagnosis of Chlamydia trachomatis by the probe amplification method, LCR (ligase chain reaction) has been shown to be both sensitive and specific. Nucleic acid sequence based amplification (NASBA) has been applied to the identification of mycobacteria using universal primers, with subsequent species-typing with specific probes. Strand displacement amplification (SDA) has been described for the detection of *M tuberculosis.*

Methods are available for the detection of *M. tuberculosis* complex in respiratory secretions and *C. trachomatis* in urethral swab specimens and urine.

Fungi

Rapid diagnosis of disseminated candidiasis and invasive aspergillosis could be improved by molecular methods. Highly conserved ribosomal DNA (rDNA) targets have been used as non-genus specific targets for PCR amplifications.

PCR detection can also be used to monitor therapy. The use of 5S rDNA probes in a PCR amplification assay to detect *P. carinii* in sputum samples from AIDS patients was used to monitor treatment with pentamidine. The shedding patterns correlated consistently with clinical outcome even though the organisms were not reliably detected by cytology.[5] The specificity of PCR for the detection of P carinii is high, but its sensitivity is also high, higher than immunofluorescence, and in one study the organism was detectable in the absence of clinical symptoms.[6]

Other Specific Technologies

The standard technique for rapid diagnosis by using immunofluorescence should not be forgotten. Although less sensitive than the molecular techniques described, they are well-established and are useful rapid screening tools for respiratory viruses.

Direct antigen detection methods are available and used for a number of bacterial pathogens, including Strep. pneumoniae and other streptococci. These are reported to have a sensitivity of 60-95%, relative to culture, with adequate training in their use, a key to minimizing both false negatives and positives. In many laboratories, a dual swab/specimen system is used, one for direct antigen detection and another for routine culture.

ELISPOT (enzyme-linked immunospot) assays which detect antigen-specific T-cells are also coming out of research laboratories. One assay to detect *M. tuberculosis* is reported to allow earlier detection than the tuberculin skin test.[7] These assays are quantifiable and have the potential to be automated for epidemiological screening.

Flow cytometry[8] is a method whereby a specimen is passed through a 'capture' system that results in a detectable signal. Antigen, antibody or nucleic acids can be captured and depending on the signal used, common examples being fluorescence and change in electrical impedance, can be quantified. It has also been adapted for antimicrobial susceptibility testing. It has been applied to the detection of several viral and bacterial respiratory pathogens but primarily in a research setting. Although it is possible to obtain results within 4 hours, the method is still hampered by specificity issues and the costs of setting up the technology.

Non-invasive Markers

Non-specific markers of airways inflammation are being evaluated to allow early detection of inflammation of the lower respiratory tract, particularly in those at-risk patients with chronic lung disease, which may be signal infection. The most studied of these is the measurement of exhaled gases such as nitric oxide (NO), carbon-monoxide (CO), ethane, pentane and non-volatile substances in breath condensate such as hydrogen peroxide.

An example would be high levels of exhaled NO which seem to occur in exacerbations of chronic obstructive pulmonary disease (COPD). This rise in NO levels occurs in both viral and bacterial infections: indeed there is often a rise in viral upper respiratory tract infections in patients without COPD.[9] Nasal NO rises have also been used as markers of nasal inflammation in allergic rhinitis and could also be used as a beacon of upper respiratory tract viral infection although this has not yet been reported.

The analysis of breath condensate where a patient breathes through a mouth piece into Teflon tubing, that is connected with a dry ice container also offers utility as a non-specific marker. The 1 ml of breath condensate that can usually be collected after 5 min of breathing can be assayed for inflammatory mediators such as tumour necrosis factor and interteukin-1. This has not yet been applied to the early diagnosis of infection *per se*, but there have been short reports of studies in detecting early inflammation in asthma and COPD.

CONCLUSIONS

Nucleic acid probes are becoming a standard diagnostic methodology in microbiology Evaluation studies are already showing that for many micro-organisms they are cost-effective when compared to standard cultural and serological methods. Automation is the key to the high through-put and rapid turnover of specimens that will be required. This will not only lead to a more specific and sensitive detection of micro-organisms, but drive down the financial costs of molecular diagnostics. The next major advance will be the incorporation of DNA chip technology into routine diagnostics. Probes are bound to a solid phase for detection of unknown, 'interrogated', DNA.

The pace of laboratory diagnosis is possibly greater than in other areas of clinical practice. The future is likely to be focused on rapid, automated tests.

KEY POINTS FOR CLINICAL PRACTICE

- **Adequate specimen collection and transport are an essential part of rapid microbiological diagnosis.**
- **Consider more than one specimen sample to enable several techniques to be applied.**
- **Laboratory methods are automated and should enable faster results.**
- **It is essential to understand the basis of the new technologies if the correct interpretation is to be made of the result.**

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CHAPTER

26

HIV Disease and Respiratory Infection in Children

Praveen Khilnani

Over one million children world-wide are living with HIV (human immune deficiency virus) infection and respiratory disease is the commonest cause of morbidity and mortality in these children.[1,2] The initial presentation of respiratory infection is usually in infancy or early childhood. There is enormous potential to prevent childhood HIV infection that is being realised in industrialised countries.

Most childhood HIV infection is vertically acquired and the first clinical presentation of HIV-related pneumonia is usually in infancy or early childhood.

Incidence of Childhood HIV Infection

By the end of 2000, UNAIDS (World health organization) estimated >34 million cases world wide, >10 million in india. 1.4 million children were living with HIV of whom approximately 600,000 were infected during, 2000 alone, and 4.3 million had already died.[3]

Over 90 percent of infected children each year are from Africa which is home to over two-thirds of HIV-infected persons.[3] India is rapidly emerging as a country with a high number of undiagnosed HIV cases. Although contributing less than 1 percent of children infected with HIV world-wide, there are currently around 15,000 children living with the disease in the US and Western Europe. In all parts of the world, most HIV in children is acquired from mother-to child transmission (vertical transmission),[4] although in some areas, such as Romania, large numbers of children were infected through contaminated blood/blood products in the late 1980s.

The rate of mother-to-child transmission prior to the advent of interventions in Europe and the US was around 15-20 percent, compared with around 30 percent in Africa. Most of this difference is accounted for by breastfeeding which accounts for about one-third of transmission in Africa. Since 1995, mother-to-child transmission rates have decreased dramatically, due to wide-spread implementation of interventions including refraining from breastfeeding, the use of antiretroviral therapy for the mother and newborn and elective Cesarean section delivery.[5-8] Mother-to-child transmission rates below 1 percent are currently reported among women on potent ART (Anti retroviral therapy) therapy with undetectable HIV viral load at delivery. Guidelines recommending the universal provision of antenatal HIV testing have been developed and implemented successfully in most Western countries.[9] Thus, new pediatric HIV infections in industrialised countries are increasingly in children from countries with a high prevalence of HIV infection. In the UK, over 75 percent of sero-positive newborns are delivered to mothers born in sub-Saharan Africa, and approximately one-third of HIV infected children were themselves born overseas.[10]

As in industrialised countries, almost all childhood HIV infection in non-industrialised countries is acquired perinatally through mother-to-child transmission (Table 26.1). In stark contrast, however, vertical transmission rates are around 30 percent.

Table 26.1: Key differences in the manifestations of HIV between adults and children (vertical transmission) are as follows:

1. HIV antibody tests cannot be used to diagnose infection in infancy
2. Faster rate of clinical disease progression in some children; 20-25 percent progress in the first year in the absence of antiretroviral therapy and PCP prophylaxis
3. Primary disease with opportunistic infections more common than re-activation
4. Lymphocytic interstitial pneumonitis (LIP) is common
5. Bacterial infections are very common and occur at all stages of disease HIV encephalopathy presents differently
6. Growth failure occurs as well as weight loss and wasting Kaposi's sarcoma is rare outside endemic areas
7. Patterns of CD4 cell count and HIV-1 RNA viral load are different.

Antenatal care is often in adequate, maternal HIV status is usually not known, very few women have access to interventions and breast-feeding is almost universal. In the last 2 years, breakthrough clinical trials have demonstrated the efficacy of low cost ART regimens to reduce mother-to-child transmission, including the perinatal use of single dose Nevirapine to the mother and neonate. Data from this Ugandan trial suggested that 35-40 percent reduction in mother-to-child transmission could be maintained at 12 months even among breast-feeding women.[11] Thus, in the last year, a number of implementation programs have been established in African countries to undertake antenatal HIV testing and to offer ART to women to reduce mother-to-child transmission. Major implementation barriers including poor infrastructure exist in most countries and the issue of breast-feeding is unresolved. Breast-feeding results in about one-third of mother-to-child transmission in Africa, but alternatives to breast-feeding remain expensive, dangerous in the absence of clean water, and culturally unacceptable.

Diagnosis of HIV Infection in Infancy

The majority of HIV infected children can be diagnosed within the first month of life by use of DNA PCR (polymerase chain reaction) techniques. HIV antibody is of no value in the first 12-18 months of life as it is not possible to distinguish the child's antibody from maternal antibody acquired transplacentally. As PCR testing is technically difficult and expensive, the possibility of early diagnosis for HIV infected children in Africa is rarely available, and the sensitivity and specificity of clinical symptoms and signs to predict HIV infection is very limited in infancy in the African setting.[1]

HIV-related Morbidity and Mortality

In Europe and the US before the availability of antiretroviral therapy for children, around 20-25 percent progressed to AIDS or died in infancy, most commonly from *P Carinii pneumonia* (PCP). Survival rates of 70 percent by 6 years and 50 percent by 9 years were reported from prospective cohorts. In a recent analysis of over 3000 HIV-infected children participating in clinical trials in the US before highly active antiretroviral therapy (HAART) became available, serious bacterial infections (rate 15.1/100 child-years; most commonly pneumonia 11/100 child-years) which occurred during all stages of HIV infection, and PCP (1.3/100 childyears) and mycobacterium avium-intracellulare complex (MAIC) (1.8/100 child-years), which occurred in advanced disease, were the most common infections.[12] These occurred at much higher rates than among HIV-negative children. Since 1997, the availability of HAART has led to a dramatic reduction in HIV disease progression, morbidity requiring hospital admission, and death.[13] Even before 1997, decreased progression rates were reported, attributed, in part, to the availability of double ART.[14] Further, the revised guidelines for PCP prophylaxis in 1995[15] and intensive regimens for management of children with lymphocytic interstitial pneumonitis (LIP) and recurrent chest infections contributed to a falling incidence of PCP[8] and chronic lung disease, respectively, before the HAART era. Nonetheless, a quarter of children living with HIV are now entering teenage years and some have residual damaged lungs from respiratory illness in early childhood which HAART may not improve.

Causes and Management of Respiratory Infections (Table 26.2)

Bacterial Pneumonia

The respiratory tract is the most common site of bacterial infections, with approximately half being lower respiratory infections. Bacterial pneumonia

Table 26.2: Common causes of respiratory infection in HIV-infected African children

Organisms	*Age group*	*Impact of HIV infection*
Bacterial pneumoniae		
Streptococcus pneumoniae	All ages	Increased incidence
Hemophilus influenzae		Early relapse and higher case-fatality rate in those with ARDS
Staphylococcus aureus		Increased antibiotic resistance
Klebsiella spp.		
Salmonella spp.		
Escherichia coli		
Pseudomonas aeruginosa		
Pneumocystis carinii	2-6 months	Very strongly HIV-related Common cause of death in HIV-infected infants Poor outcome, especially if associated with CMV infection
Viral pneumonia		
Respiratory syncytial virus	Infants	Higher rates and more secondary bacterial pneumonia Less wheeze or typical bronchiolitis Higher mortality
Cytomegalovirus	Infants	Under-recognised No treatment available in Africa
Measles	Usually after 6 months	More common More severe
Lymphocytic interstitial pneumonitis		
Epstein-Barr virus	Usually after 1 year	Always HIV-related Better prognosis group Often confused with TB Increased recurrent chest infections and bronchiectasis
Pulmonary tuberculosis		
Mycobacterium tuberculosis	All ages	More common Diagnosis more difficult Tuberculin test less sensitive Poorer outcome
Bronchiectasis		
Secondary to above infections	Usually after 3-4 years	
Pulmonary Kaposis sarcoma		
Human herpes virus 8	Usually after 3-4 years	Strongly HIV-related
Nocardiosis		
Nocardia asteroides		Confused with PTB

was common in HIV-infected children in the US before the era of HAART and was more frequent than pneumonia due to opportunistic pathogens such as *P carinii* even before the routine use of PCP prophylaxis with Cotrimoxazole[12,16] (Trimethoprim-sulfamethoxazole).

Bacterial pneumonia, particularly due to *Streptococcus pneumonie* was 5-10 times more common in HIV-infected than in HIV-uninfected children in the US and Europe.[12,17] Bacterial pneumonia also occurs, albeit less frequently, in children with relatively high CD4 cell counts, suggesting that serious bacterial infections occur at all stages of HIV infection.[12] In addition, pneumonia has been reported with approximately twice the frequency in children with underlying LIP,[17] with many children having repeated hospital admissions for lower respiratory tract infections. Other bacterial pathogens include *Hemophilus influenzae, Staphylococcus aureus* and *Salmonella species.*

The incidence of bacterial pneumonia and associated mortality was already high in non-industrialised countries prior to the HIV epidemic and the commonest cause was Strep. pneumoniae.[18,19] Similarly, the commonest isolate from blood culture of HIV-infected African children hospitalized with severe pneumonia is Strep. Pneumoniae.[16-23] A recent study from South Africa estimated the risk of invasive pneumococcal disease to be 40 times greater in HIV-infected children than in HIV-uninfected children.[20] The range of other bacteria causing pneumonia in HIV-infected children is similar to that in HIV-uninfected children but also with greater frequency. *Staph. aureus* has re-emerged as an important cause of pneumonia in South African children with HIV infection, particularly among those with a history of chronic lung disease.[16,21] Salmonella is an important invasive pathogen in tropical Africa particularly during the rainy season and is often HIV-related.[16,22]

Gram-negative bacteria such as *Klebsiella pneumoniae* and *Escherichia coli,* which are common in malnourished children without HIV infection, are also common in HIV-infected children.[1,20,21] Although the case-fatality rate for severe acute pneumonia is up to 6 times higher than in HIV-uninfected children, this mainly reflects the impact of *P Carinii pneumonia* (PCP).[16-22] HIV-infected children are also prone to recurrent bacterial disease and infection with antibiotic resistant organisms. However, *in vitro* resistance does not necessarily affect treatment response for bacterial pneumonia.

In addition to prompt treatment with antibiotics, physiotherapy and nutritional support for those with chronic lung disease, strategies to reduce or prevent bacterial infections in general, and pneumococcal disease in particular, are a priority. *H. influenzae* type b (Hib) conjugate vaccine is now routinely given to children in most well-resourced countries and a study in the pre-HAART era showed that most HIV-Infected children achieve Hib antibodies in the protective range, although levels were 10-fold lower than in HIV-uninfected children, and even lower in children with AIDS.[23] Polysaccharide pneumococcal vaccine has been recommended for HIV-infected children, but there are no data from phase III trials and results of a Ugandan trial showing poor efficacy in HIV-infected adults is of concern.[24] Pneumococcal conjugate vaccines may prove to be an important intervention for pneumococcal disease in HIV-infected children, even in the era of HAART, given the efficacy of this vaccine in preventing pneumococcal disease in normal children in clinical trials.[25] Data are eagerly awaited from a current trial of a pneumococcal conjugate vaccine in South African children where HIV infection is common.

Pneumocystis Carinii Pneumonia (PCP)

There is now robust evidence from autopsy and clinical studies that PCP is a common cause of severe pneumonia and death in HIV-infected African infants.[17,26] PCP should be suspected in an infant between 2-6 months of age with marked respiratory distress, often with severe hypoxia, a poor response to standard first-line antibiotics and either a clear chest or diffuse rather than focal abnormalities on auscultation.[1] The hypoxia is less responsive to oxygen than is bacterial pneumonia.[22] PCP is a clinical diagnosis as confirmation requires technology such as fluorescent microscopy or PCR of broncho-alveolar secretions or nasopharyngeal aspirates and these are rarely available. The most common abnormalities on chest radiograph are hyperinflation or a diffuse interstitial pattern but these are non-specific.

Recommended treatment includes high-dose intravenous (or oral if not available) Cotrimoxazole, prednisone and oxygen but outcome is very poor.[22] Data from South Africa suggest that CMV (Cytomegalovirus) pneumonitis not uncommonly occurs with PCP.[14] The outcome for these infants is even worse than among those with PCP alone, and there is suggestive evidence that administration of steroids may worsen CMV pneumonitis.[4,27] As mixed infections are common in HIV-infected children, initial treatment should include a recommended antibiotic for severe bacterial pneumonia even when PCP is strongly suspected.[1]

In resource-rich countries, PCP also presents most commonly in the first 6 months of life and before the era of HAART, had a very poor outcome, despite availability of intensive supportive care with ventilation, intravenous high dose Cotrimoxazole and steroids.[28-33]

CD4 count was shown to have limited value in predicting development of PCP in infants, which often occurred even before the diagnosis of HIV. The recognition of this led to the 1995 revised guidelines recommending universal Cotrimoxazole prophylaxis in all infants born to infected women from 6 weeks of age irrespective of CD4 cell count.[15] This has contributed to the reduced incidence of PCP observed even before the advent of HAART.[8]

Infants who recover from PCP can now expect to do very well clinically with normal development and growth, good recovery of CD4 cell numbers and often undetectable viral load on HAART. This contrasts with previous experience where children surviving PCP often went on to develop HIV encephalopathy and other AIDS indicator diseases. However, even in the era of HAART, some babies with PCP will die of their initial lung disease before HAART can be given,[4] stressing the value of diagnosing HIV in women antenatally. In the UK, PCP has also been reported to occur frequently with CMV disease in infants, the occurrence of dual infection being independently associated with breast-feeding and with mothers being born in Africa.[4] Survival was significantly worse for infants with dual infection and, in contrast to previous studies, use of adjuvant Corticosteroids was not associated with improved survival from PCP. This finding may be partly explained by the high prevalence of CMV co-infection in this study, as Corticosteroids could adversely affect the course of CMV disease. These data suggest that infants developing PCP should be investigated for CMV infection and retinitis, especially if they were born to African mothers and were breast-fed. In addition, anti-CMV therapy with gangcyclovir should be strongly considered in infants with PCP and evidence of CMV infection, especially in those who receive adjuvant Corticosteroids.

Prophylaxis against PCP and Bacterial Infections

In Europe and the US, Cotrimoxazole is recommended for primary prophylaxis against PCP in children born to HIV-infected women, starting at 6 weeks of age and continuing until HIV infection status is shown to be negative.[15] In infected children, it is recommended to stop after 12 months of age, if the CD4+ cell count is over 750 cells/mm' or 15 percent of total lymphocyte count. In Africa, UNAIDS recently made a recommendation that infants born to HIV-infected women should receive Cotrimoxazole prophylaxis, as in the industrialized world.35 However, the majority of HIV-infected women currently remain undiagnosed, and although this strategy has been introduced with antenatal HIV testing programs in some areas of Africa, this not yet standard practice in most regions. No trials have evaluated the efficacy of Cotrimoxazole prophylaxis in reducing bacterial and other infections in children after the first year of life. In the early 1990s, two trials of intravenous immune globulin (IVIG) therapy in children reported reductions in the number of bacterial infections and hospital admissions in the IVIG arm, but no effect on HIV progression or survival.[34,35] This expensive and difficult therapy is no longer recommended for HIV-infected children.

Viral Pneumonia

HIV infection is associated with an increased frequency and poorer outcome with viral pneumonia such as due to respiratory syncytial virus (RSV), influenza, parainfluenza, adenovirus and measles.[36,37] Characteristics of RSV infection in HIV-infected children are that the typical presentation of bronchiolitis with wheeze is less common while secondary bacterial pneumonia is more common and there is a higher case-fatality rate than in HIV-uninfected children.As mentioned Cytomegalovirus (CMV) may occur with PCP4 and was a common finding at autopsy in the lungs of HIV-infected infants. CMV was cultured from respiratory secretions from 14 percent of HIV-infected children with severe pneumonia in Cape Town. HIV-infected children with immunosuppression may develop giant cell pneumonia due to varicella, although this is rare in early stages of HIV. Autopsy and clinical studies have found that mixed viral and bacterial pneumonia is common.[1,21,36]

Pulmonary Tuberculosis

HIV-infected children are susceptible to tuberculosis (TB) but the incidence of TB is low in the US and Europe compared to other HIV-related disease.[12-15] TB is much more common in Africa than in the US or UK and the numbers are increasing because TB control among adults has worsened. Further, there is now good evidence that in regions where childhood HIV infection is common, HIV prevalence is high among children with TB, including those with confirmed PTB (Pulmonary TB).[20,21,38,39] The extent of TB/HIV co-infection in children varies between regions and important factors include childhood HIV prevalence, the severity of the TB epidemic among the adult population and the prevalence of TB/HIV co-infection in adults.

The clinical presentation of PTB and radiographic abnormalities are similar in HIV-infected and HIV-uninfected children.[1,38,39] The tuberculin test is less sensitive but may still be useful. Response to anti tuberculosis therapy may be poorer in HIV-infected children, particularly in those with advanced disease'. Thiacetazone should not be used as there is a high risk of a severe and often fatal Stevens-Johnson reaction. The value of prophylaxis given to HIV infected household contacts of cases of smear-positive PTB has not been studied. None-the-less, giving isoniazid prophylaxis to young children in households with open PTB would be desirable.

M. tuberculosis has been reported infrequently in HIV-infected children in Europe or the US. However, PTB has been reported as the most common AIDS diagnosis in adults in the UK who acquired HIV in Africa, and children of these adults are clearly at risk. The question of BCG (Bacille Calmette-Guerin) vaccination for babies of immigrant African mothers with HIV has been debated in the UK. While the risk-benefit ratio would favor routine BCG in babies irrespective of the HIV status of the mother in the African setting, the balance would be against it in most parts of Europe and the US where the risk of BCG-osis, although small, is present for babies with rapid disease progression. However, in parts of the UK, with large African immigrant populations, and where children may be likely to travel back to Africa, the benefit may outweigh the small risk to the infected child. BCG immunization is almost universal in African countries and yet BCG disease is rare even in HIV endemic regions.

Non-tuberculous mycobacterial infections are uncommon in the era of HAART and only occur with very low CD4 cell counts. The most common organism in this group is MAIC (mycobacterium avium intracellulare) which causes around 90 percent of identified infections.[40] It usually presents with systemic disease and rarely as respiratory disease alone. Respiratory distress with nodular infiltrates on CXR (chest X-ray) may occur.

Table 26.3: Lymphocytic interstitial pneumonitis in HIV-infected children

1. Occurs in 25-30 percent of vertically HIV-infected children but is rare in those infected through other routes at an older age, and in adults.
2. Associated with a better prognosis than many other HIV manifestations.
3. Associated with parotid enlargement and marked lymph-adenopathy. May be associated with obstructive airways disease (which may respond to bronchodilators).
4. Secondary bacterial infections and bronchiectasis occur, but wide variation from asymptomatic to severely hypoxic.
5. May be associated with obstructive sleep apnea and adenoidal and tonsillar hypertrophy.
6. Hyperviscosity associated with very high immunoglobulin values may occur.
7. Has been associated with MALT (mucosa-associated lymphoid tissue) but this is rare and does not necessarily have a poor prognosis.

Lymphocytic Interstitial Pneumonitis (LIP)

Lymphocytic interstitial pneumonitis (LIP; Table 26.3) is characterised by extensive lymphocytic infiltration of the pulmonary interstitium. It occurs almost exclusively in HIV-infected children and Epstein-Barr virus (EBV) is thought to be important in the pathogenesis. LIP usually present after 2 years of age and is common in African children.[1,39,41] LIP presents with a broad spectrum of clinical and radiological disease and is often confused with TB. Thus, many children present with chronic respiratory disease but a poor response to anti TB therapy. Clinical features that are often associated with LIP include generalized and symmetrical lymphadenopathy, bilateral chronic non-tender parotid swelling, digital clubbing and hepatomegaly. Typical radiographic findings are diffuse bilateral reticulonodular infiltrates so it can be misdiagnosed as miliary TB.

Confirmation of diagnosis requires a lung biopsy which is rarely undertaken. Lung histology shows considerable changes in lung architecture with invasion of alveoli with CD8 cells. A bronchoscopy study with biopsy of South African children found that LIP was the most common abnormality in HIV-infected children with chronic respiratory symptoms and was more common than PTB.[41] Unlike PCP, LIP is associated with a favourable prognosis but secondary bacterial pneumonias and eventual bronchiectasis are common. This further confuses interpretation of chest radiographs. Corticosteroids, although not subjected to a controlled trial, appear to be effective in alleviating respiratory symptoms and are used for 4-6 weeks in high doses, followed by rapid weaning to small alternate day doses. It is important, therefore, to exclude PTB in these patients and to consider TB prophylaxis. As HIV disease progresses, features of lymphocytic infiltration such as lymphadenopathy and parotid swelling diminish as the child's immune function worsens and he/she becomes more wasted.

In Europe and the US, LIP has been reported to occur in approximately 20-30 percent of vertically HIV infected children, but is rare in adults with HIV. Anecdotally, in these countries, it appears to be more common in children of African origin (possibly associated with an earlier acquisition of EBV). Recurrent bacterial and viral respiratory infections appear to be more common in association with LIP, but children may manifest a range of symptoms from asymptomatic to chronic hypoxia. In addition to steroids, ART improves symptoms and radiographic appearances of LIP. It is to be hoped that younger children who have had the benefit of receiving HAART before becoming symptomatic have less problems with chronic lung disease associated with LIP. Many children with LIP have associated wheezing and may also benefit from the use of a bronchodilator.

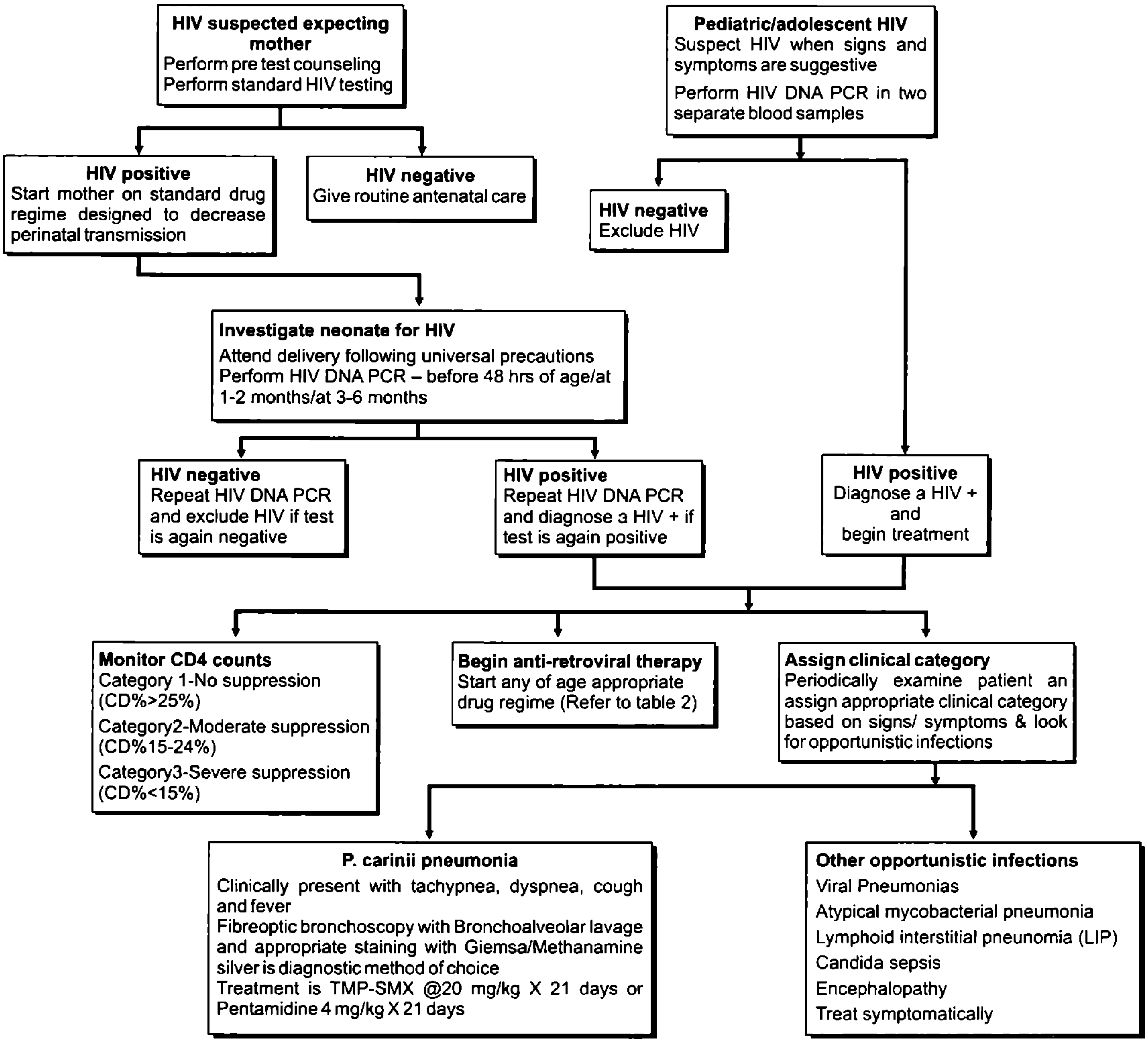
Other causes of Respiratory Disease

Malignant lymphoma has been reported to occur approximately 1000 times more frequently than in HIV-uninfected children,[42] and as in adults with HIV, a decline with the advent of HAART may occur. Lymphomas are usually of the B-cell type and most frequently affect the brain, but have also been reported in the nasopharynx, soft palate, and tonsilliar areas. In a case-controlled study in Uganda, Burkitt's lymphoma was 7.5 times more common in HIV-infected compared with uninfected children, and HIV infection was associated with a considerable increase in risk from Kaposi's sarcoma (OR 94.9), which in this endemic form, may also affect the lungs.[43] Mucosa-associated lymphoid tissue has been reported in association with LIP, but this is rare.

SUMMARY (FLOW CHART 26.1)

This chapter has emphasised the importance of respiratory infections in HIV-infected children. Common causes of acute pneumonia include the usual respiratory pathogens of childhood such as pneumococcus or RSV that occur more frequently and more severely, and opportunistic pathogens such as *P Carinii* and CMV, that are often fatal. LIP is a common cause of chronic, recurrent respiratory disease in HIV-infected children and PTB is common in regions of high TB endemicity. The implementation of preventive strategies has successfully and dramatically reduced mother-to-child transmission of HIV infection in industrialised countries, and the incidence of PCP in HIV-infected infants. The advent of potent ART has increased survival and changed the pattern of morbidity. Although not as well documented, data are emerging that suggest that the pattern of respiratory infections in HIV infected children in the non-industrialised world is not markedly different from that which occurred in the industrialised world before ART was available and PCP prophylaxis to HIV-exposed infants was routine. The major differences from well-resourced countries are the scale of the problem, the frequent early morbidity and poor survival, the limited diagnostic and therapeutic options, and the inadequacy of the health care infrastructure to implement effective prevention strategies. It is to be hoped that with the recent call for therapies for HIV to be made available at affordable prices in resource-poor countries most heavily affected by HIV, that implementation programs and the necessary infrastructure both to reduce mother-to-child transmission and to provide, sustainably, treatment for HIV-infected children and adults will be a priority for governments, international organisations and research institutions around the world.

Flow chart 26.1: Approach to pediatric HIV


HIV suspected expecting mother
Perform pre test counseling
Perform standard HIV testing
HIV positive
Start mother on standard drug regime designed to decrease perinatal transmission
HIV negative
Give routine antenatal care
Pediatric/adolescent HIV
Suspect HIV when signs and symptoms are suggestive
Perform HIV DNA PCR in two separate blood samples
HIV negative
Exclude HIV
Investigate neonate for HIV
Attend delivery following universal precautions
Perform HIV DNA PCR – before 48 hrs of age/at 1-2 months/at 3-6 months
HIV negative
Repeat HIV DNA PCR and exclude HIV if test is again negative
HIV positive
Repeat HIV DNA PCR and diagnose a HIV + if test is again positive
HIV positive
Diagnose a HIV + and begin treatment
Monitor CD4 counts
Category 1-No suppression (CD%>25%)
Category2-Moderate suppression (CD%15-24%)
Category3-Severe suppression (CD%<15%)
Begin anti-retroviral therapy
Start any of age appropriate drug regime (Refer to table 2)
Assign clinical category
Periodically examine patient an assign appropriate clinical category based on signs/ symptoms & look for opportunistic infections
P. carinii pneumonia
Clinically present with tachypnea, dyspnea, cough and fever
Fibreoptic bronchoscopy with Bronchoalveolar lavage and appropriate staining with Giemsa/Methanamine silver is diagnostic method of choice
Treatment is TMP-SMX @20 mg/kg X 21 days or Pentamidine 4 mg/kg X 21 days
Other opportunistic infections
Viral Pneumonias
Atypical mycobacterial pneumonia
Lymphoid interstitial pneunomia (LIP)
Candida sepsis
Encephalopathy
Treat symptomatically

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CHAPTER

Acute Respiratory Distress Syndrome (ARDS) in Children

Praveen Khilnani, Prabhat Maheshwar

INTRODUCTION

Acute respiratory distress syndrome (ARDS) is a clinical syndrome of acute respiratory failure following almost any severe physiologic insult that may or may not have injured lungs primarily. The hallmark of the syndrome is increased permeability of the alveolar-capillary membrane, resulting in pulmonary edema.

Common precipitating factors include shock of any etiology, sepsis, viral or bacterial pneumonia, trauma, aspiration pneumonia, near drowning and ingestions (Table 27.1).

Table 27.1: Etiological agents for ARDS

Nonpulmonary causes
Trauma
Drug Overdose
Sepsis
Narcotic Idiosyncrasy
Pancreatitis
Near Drowning
Cardiopulmonary Bypass
Massive Transfusion
Shock
Disseminated Intravascular Coagulopathy
Hemodialysis
Burns
Fat Embolism

Pulmonary causes
Smoke Inhalation
High Altitude
Strangulation
Infectious Pneumonia (Gram negative, Viral, Pneumocystis)
Aspiration Pneumonia, Toxic Gas Inhalation

It was first described as a distinct entity in 1967 by Ashbaugh et al[1] in adults. The pathologica appearance on lungs was similar to that of respiratory distress syndrome of the neonates and the term "Adult" respiratory distress syndrome was used to describe similar condition in older patients. ARDS is now known as acute respiratory distress syndrome. Early reports of ARDS involved severe hypoxemia but the pathophysiological alterations of ARDS can occur across a wider range from mild to severe pulmonary dysfunction. More important is recognition of the similarities among ARDS, sepsis post traumatic hyper metabolism, and multi organ failure in terms of clinical overlap, mediator release and mechanism of tissue injury.[3,4,5] Lungs bear the brunt of injury possibly because of receiving the entire cardiac output with exposure to circulating agents as well as exposure to environmental insults during ventilation. The lung may also have a unique interaction of cells as part of the mononuclear phagocyte system that makes the pulmonary microvasculature more susceptible to injury from circulating mediators.'

Pathophysiology

ARDS is a clinical syndrome characterized by severe hypoxemia, respiratory distress, altered respiratory mechanics and effects on cardiopulmonary interaction.

Pathophysiologically it is an evolving process and can result from a wide range of diseases and precipitating factors as mentioned in Table 27.1.

This means that while initiating biochemical event may vary e.g. endotoxins in infection, oxidant production in ischemia or compliment activation in antigen-antibody mediated reaction, but eventually all endogenous protective systems including cytokine release, lipid mediator release and compliment activation of coagulation system are involved in development of ARDS. The activation of cascade of inflammatory mediators results in 'diffuse alveolar damage'.[6]

Pathologically this process can be divided into 3 phases -

1. Exudative phase: This is early phase and occurs in first week of illness. It is characterized by necrosis of type 1 epithelial cells and disruption of capillary membrane resulting in oedema formation.
2. Proliferative phase: This phase begins as early as third day but is most prominent one week after the onset. It is characterized by proliferation of type 2 cells, an interstitial mononuclear inflammatory infiltrate and organization of hyaline membrane.
3. Fibrotic phase: This phase is established by 3 to 4 weeks of illness. The process of fibrosis starts with deposition of type 3 collagen, which is later replaced by more rigid type 1 collagen, and results in stiff lungs.

Physiological Derangements in ARDS

The hallmark of ARDS is increased permeability of the alveolar capillary membrane with development of interstitial and alveolar edema that results in decreased pulmonary compliance, decreased functional residual capacity, and increased dead space. Pulmonary hypertension and rise in airway pressure result in increased intrathoracic pressure. This in turn decreases lymphatic flow which may further exacerbate edema formation.[7] The primary alteration in gas exchange is a large intrapulmonary shunt which results in severe hypoxemia which shows little response to increased oxygen concentration; $PaCO_2$ is usually low because of secondary hyperventilation in early ARDS. Greatest abnormalities are noticed in dependent regions of lungs.[8] The reduced lung volume available for ventilation is a major factor in reduced pulmonary compliance. Apical lung regions, spared from edema accumulation are susceptible to barotrauma and air leak commonly seen in ventilated patients with ARDS. In late ARDS, a diffuse fibroproliferative disease is often associated with localized emphysematous lesions and airway obstruction. These changes are similar to broncho-pulmonary dysplasia.

Decreased performance of right and left ventricles may occur from ARDS itself and from application of increased airway pressure. Decreased venous return is a well documented problem. Right ventricular dysfunction may occur from increased after load due to pulmonary vasoconstriction, and possibly from myocardial depressant factor induced negative inotropic effect in patients with septic shock. Left ventricular dysfunction, in turns occurs due to septal shift to left caused by right ventricular dilatation as well as global myocardial depression in patients with sepsis induced ARDS.

In summary, in this syndrome of systemic inflammatory response (SIRS), alterations occur in cardiac output, arterial oxygen content and tissue oxygen delivery. All of these are suboptimal in presence of increased metabolic demands, resulting in further tissue ischemia, lactic acidosis resulting in multi system organ failure.

Incidence

The incidence of ARDS is from 1 to 3 percent of PICU admissions in the western countries Exact incidence in Indian settings is unknown. At IP Apollo Hospital Delhi, during year 1998 to 2000, incidence of ARDS was 3 percent.

Clinical Course

The clinical course of ARDS tends to follow typical pattern, with four phases:

Acute Injury,
Latent Period,
Acute Respiratory Failure and
Severe Physiological Abnormalities

In early ARDS the lung shows pulmonary edema due to leaky capillaries. Late ARDS is characterized by a chronic, fibroproliferative lung disease.

Acute Injury

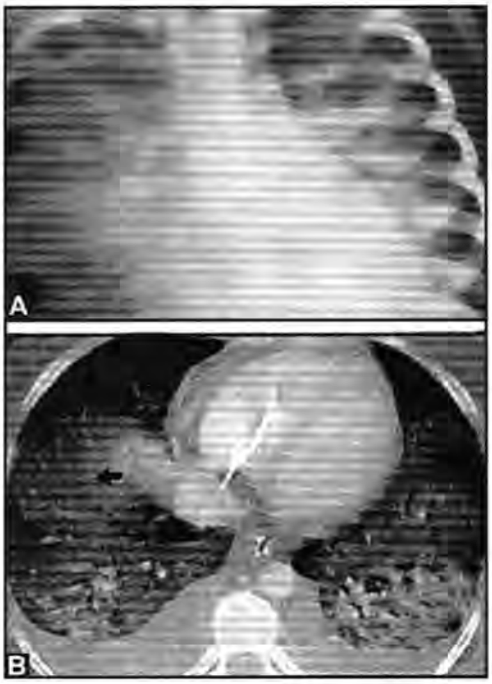
Clinical findings in the early phase are related to primary insult and there may be no apparent pulmonary dysfunction unless lungs are primarily involved.

Latent Period

For approximately 6 to 72 hours after acute injury, the patient appears to be stable or recovering. Some patients hyperventilate with a respiratory alkalosis despite adequate PaO_2 values, and the chest X-ray film may show fine reticular infiltrates consistent with interstitial fluid.

Acute Respiratory Failure

Clinical diagnosis of acute lung injury should be considered if the patient who has had an initiating insult and subsequently develops tachypnea, dyspnea, hypoxemia refractory to increased inspired oxygen concentration (due to shunting and venous admixture at the level of pulmonary capillaries), diffuse infiltrates on chest X-ray (see Figs 27.1A and B), and decreased pulmonary compliance (Fig. 27.1C). These changes have a rapid onset. Congestive heart failure must be ruled out as a cause of pulmonary edema.



Figs 27.1A and B: (A) Bilateral diffuse infiltrates without cardiomegaly: Noncardiogenic pulmonary edema of ARDS and (B) below showing a CT chest picture showing mid zone (with arrow) that is recruitable, anteriorly its open lung, posteriorly the lung is collapsed/consolidated

In ARDS PaO_2 /FiO_2 ratio is less than or equal to 200.

In ALI (Acute lung injury) PaO_2/FiO_2 ratio<300.

Diffuse crepts/rales may be noted on auscultation, and the chest X-ray demonstrates diffuse, hazy bilateral infiltrates due to interstitial and intra alveolar fluid with no cardiomegaly.

Decreased pulmonary compliance manifests as tachypnoea and dyspnoea requiring ventilatory support as cyanosis and desaturation appears on pulse oximetry despite administration of maximal inspired oxygen concentration. During this phase some patients succumb to causes of death other than respiratory failure, some recover, and others have progressive pulmonary dysfunction with transition to the next phase.

Severe Physiological Abnormalities

Transition to this phase is not clear and can happen in association with acute lung injury. This phase is characterized by ventilation perfusion abnormalities, impaired coagulation profile, unstable cardiovascular system as a part of worsening systemic inflammatory response syndrome(SIRS)which may progress to multiorgan dysfunction syndrome/failure.

Management of ARDS (Flow chart 27.1)

Management of ARDS is primarily supportive. A dedicated team of paediatric intensivists, nursing staff with other supportive staff in a well equipped

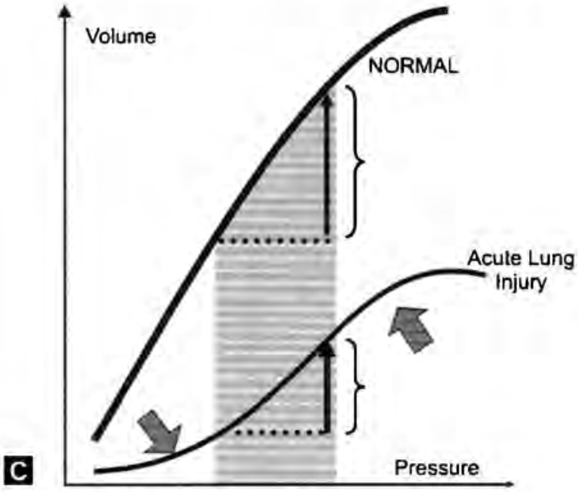
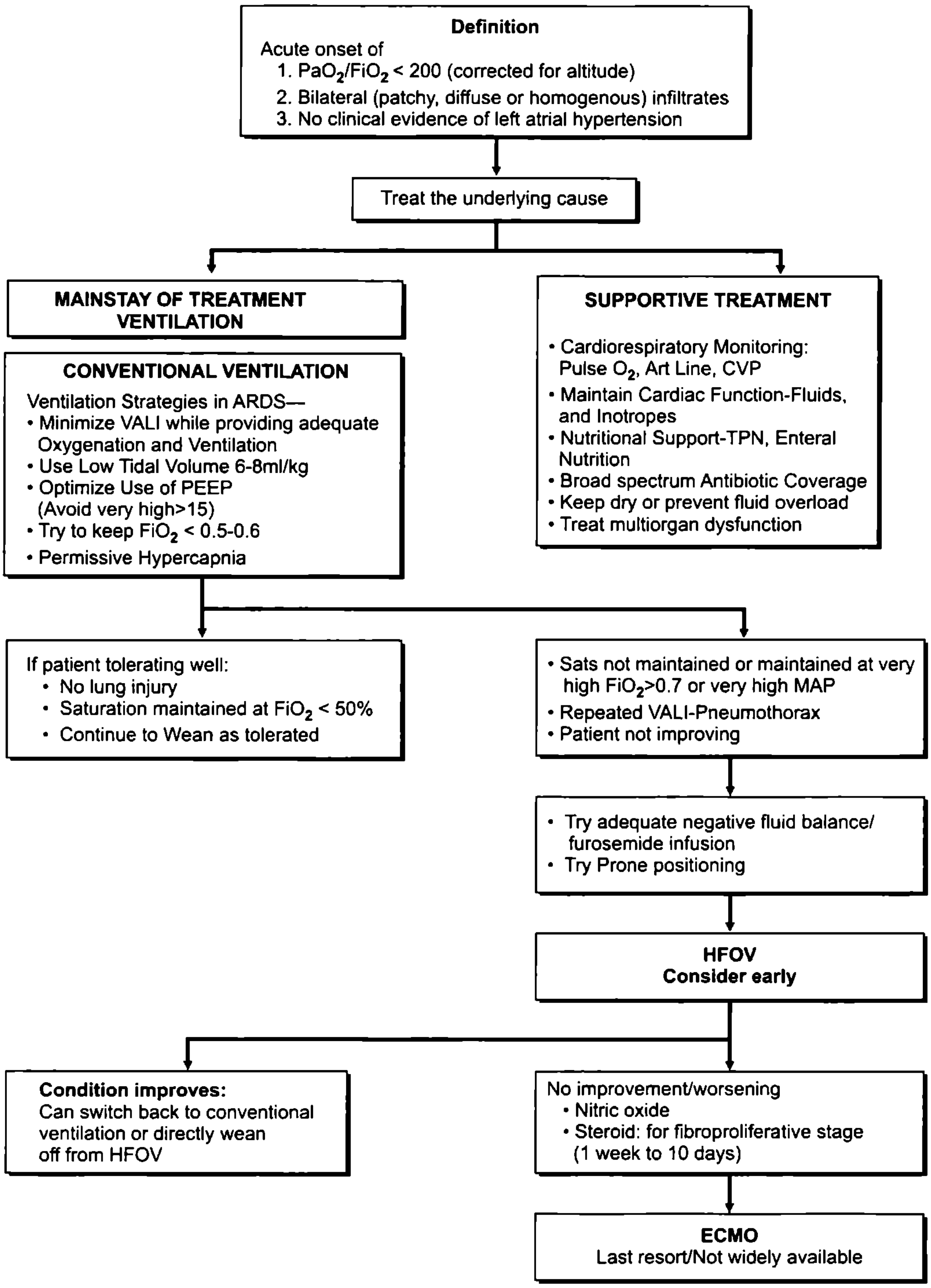


Fig. 27.1C: Pressure volume compliance curve of acute lung injury

Flow chart 27.1: ARDS Management



Definition

Acute onset of
1. $PaO_2/FiO_2 < 200$ (corrected for altitude)
2. Bilateral (patchy, diffuse or homogenous) infiltrates
3. No clinical evidence of left atrial hypertension

Treat the underlying cause

MAINSTAY OF TREATMENT VENTILATION

CONVENTIONAL VENTILATION

Ventilation Strategies in ARDS—
- Minimize VALI while providing adequate Oxygenation and Ventilation
- Use Low Tidal Volume 6-8ml/kg
- Optimize Use of PEEP (Avoid very high>15)
- Try to keep $FiO_2 < 0.5$-0.6
- Permissive Hypercapnia

SUPPORTIVE TREATMENT

- Cardiorespiratory Monitoring: Pulse O_2, Art Line, CVP
- Maintain Cardiac Function-Fluids, and Inotropes
- Nutritional Support-TPN, Enteral Nutrition
- Broad spectrum Antibiotic Coverage
- Keep dry or prevent fluid overload
- Treat multiorgan dysfunction

If patient tolerating well:
- No lung injury
- Saturation maintained at $FiO_2 < 50\%$
- Continue to Wean as tolerated

- Sats not maintained or maintained at very high $FiO_2 > 0.7$ or very high MAP
- Repeated VALI-Pneumothorax
- Patient not improving

- Try adequate negative fluid balance/ furosemide infusion
- Try Prone positioning

HFOV
Consider early

Condition improves:
Can switch back to conventional ventilation or directly wean off from HFOV

No improvement/worsening
- Nitric oxide
- Steroid: for fibroproliferative stage (1 week to 10 days)

ECMO
Last resort/Not widely available

PICU is required to manage a child with ARDS. General guidelines for management are highlighted in Table 27.2. Key issues in management involve treating the cause, to provide adequate oxygenation and ventilation while minimizing lung trauma, to improve tissue perfusion by providing hemodynamic support and taking care of fluid, electrolytes and nutrition.

Ventilatory Strategies in ARDS

It is now well known that ventilatory support provided to a patient with ARDS has the potential to worsen lung injury. This has led to development of various strategies so that we can minimize ventilator associated lung injury [VALI] while providing adequate oxygenation and ventilation.

Conventional Ventilation

Even with emergence of HFOV as a preferred mode of ventilation for ARDS, conventional ventilation is still used widely for this in India.

Concept of PEEP

The concept of using PEEP in management of ARDS is not new as it was first used by Asbaugh in 1967. Effectiveness of PEEP is more in early ARDS where it acts as a counterforce and prevents compression atelectasis secondary to pulmonary edema.[9] Pulmonary edema by increasing PVR in dependent lung regions causes redistribution of pulmonary blood flow [PBF] away from these regions. Application of PEEP may lower PVR and thus can improve V/Q matching by shifting PBF from dependent to non dependent lung regions.

Table 27.2: General guidelines for management in ARDS

1. Therapy for the initiating insult especially medical or surgical therapy for infections.
2. Cardiorespiratory monitoring-arterial line, pulse oximetcr, and central venous pressure monitoring.
3. Maintain adequate tissue oxygen delivery.
4. Support cardiac function with fluids or inotropic agents.
5. Minimize lung injury from hyperoxia and ventilation: Use PEEP and increased mean airway pressure to keep $FiO_2 < 0.50$-0.60
   Low tidal volume (6-8 ml/kg) and low end inspiratory plateau pressure (< 35-45 cm H_2O)
6. Prone positioning may be tried for improving oxygenation.
7. Other adjuncts for improvement of oxygenation such as high frequency ventilation, with or without nitric oxide, surfactant may be tried.
8. Permissive hypercapnea
9. Early, and preferably enteral nutritional support.
10. Observe for secondary infection; use broad-spectrum antibiotic coverage against gram-negative and gram positive organisms.
11. Steroid therapy in fibroproliferative phase (controversial).

An optimum level of PEEP is one which can maintain oxygen saturation to approximately 90 percent at FiO_2 of 0.5 to 0.6, however very high level of PEEP (>15 cm of H_2O) may compromise Cardiac Output by reducing systemic venous return. Adequate hemodynamic support with fluid and inotropes may help to overcome this adverse effect. PEEP is an integral part of 'Open Lung Strategy' of ventilation and optimum level of PEEP helps in reducing VALI by keeping alveoli recruited and preventing injury from repeated over stretching (Figs 27.2A to C).

Concept of Low Tidal Volume

Concept of using low tidal volume as opposed to high tidal volume has gained wide acceptance over the last decade. The aim of this approach is to minimize VALI. As ventilator induced mechanical injury is caused by repetitive over stretching and cyclic recruitment and derecruitment of collapsed areas of lung, keeping tidal volume low with optimum PEEP helps minimizing these problems.[10]

The famous ARDS network trial has shown that ventilation with a tidal volume of 6 ml/kg as

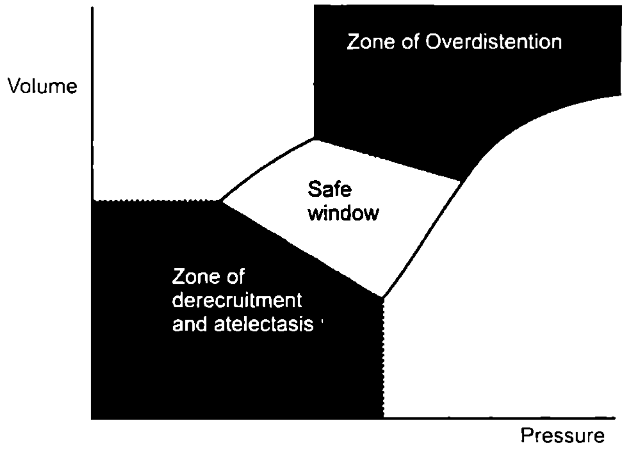


Fig. 27.2A: Open lung strategy

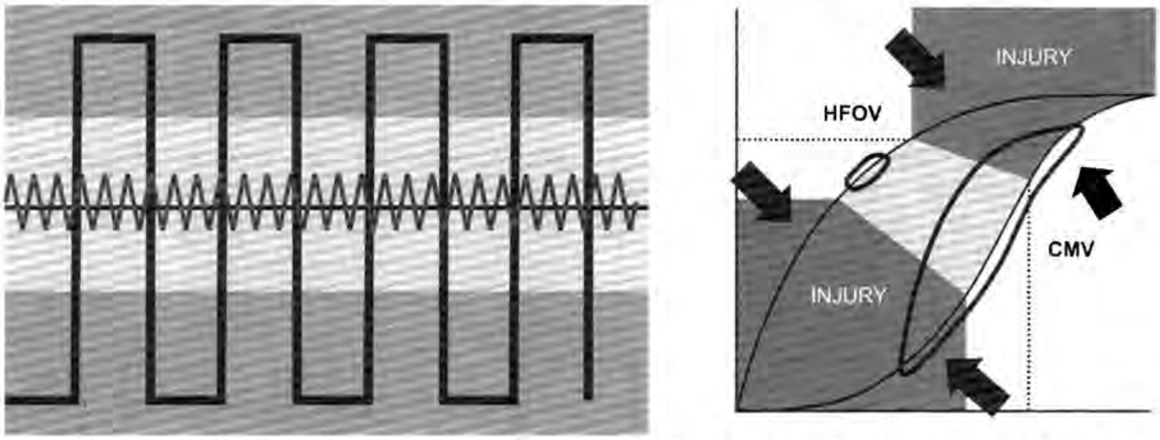


Fig 27.2B: Effect of conventional mechanical ventilation (CMV) and High frequency ventilation (HFOV) on pressure volume curve

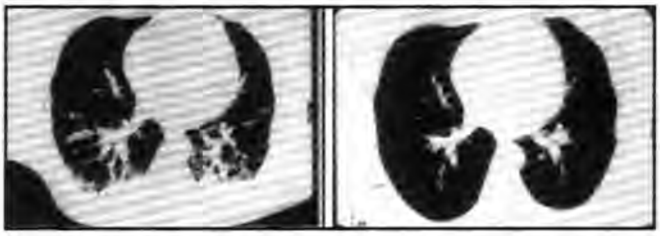


Fig. 27.2C: CT scan of chest in patient with ARDS (Left) showing basal less aerated areas and on right after recruitment of basal areas (various maneuvers including PEEP, Prone positioning) aeration is improved

compared to 12 ml/kg resulted in significant reduction in mortality as well as in ventilator days.[11]

There is limited pediatric data, however, 6-8 ml/kg seems like a reasonable tidal volume range in view of leak around the endotracheal tube in pediatric patients.

Concept of Permissive Hypercapnea and Permissive Hypoxia

Both permissive hypercapnoea and hypoxia are integral part of lung protective strategies. By allowing permissive hypoxia (keeping oxygen saturation to approximately 90 percent), we can protect the patients from deleterious effects of high FiO_2. Very high level of FiO_2 is associated with absorption atelectasis, free radical injury to lungs and systemic toxicity as well. Various animal studies have revealed that exposure to an FiO_2 of 1.0 leads to significant reduction in functional residual capacity. It also impaires mucociliary clearance.[12]

Concept of tolerating a higher level of $PaCO_2$ with maintaining pH >7.2 is directly linked with protection of lung from mechanotrauma.[13] Apart from this hypercapnoeic acidosis per se may down regulate inflammatory cell activity and may reduce oxidant stress by inhibiting xanthine oxidase.[14]

High Frequency Oscillatory Ventilation

HFOV works by oscillating lungs across a set mean airway pressure. CO_2 elimination is done by cycling a below normal tidal volume at a supraphysiological rate. The advantages of HFOV over conventional ventilation are that it provides gas exchange at a lower airway pressure and there are smaller phasic volume and pressure changes. HFOV operates with in the safe window on pressure-volume curve thereby causing less barotrauma and volutrauma (Figs 27.3 and 27.4). Studies have suggested that early intervention with HFOV may be beneficial (rather than use as a rescue measure) perhaps due to prevention of further VALI.[15]

A recent Cochrane review, which examined the effect of high-frequency ventilation compared with conventional ventilation as a therapy for ARDS in children [1 to 17 years old] and adults, revealed that there was a statistically significant reduction in the risk of requiring supplemental oxygen amongst survivors at 30 days in the paediatric study, however there was not enough evidence to conclude whether high-frequency ventilation reduced mortality or long-term morbidity in patients with ALI or ARDS.[16]

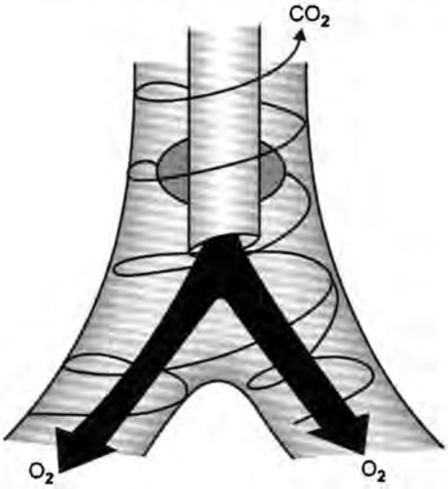


Fig. 27.3: High frequency Oscillator with schematic showing the mechanism of CO_2 removal

Fig. 27.4: Sensormedics 3100 A oscillator in use *(For color version see Plate 6)*

Prone Position

It was first advocated by Bryan in 1974.[17] It has been found that Prone positioning rapidly improves oxygenation in 70 percent of patients with ARDS, an effect that persists in 50 percent after returning to the supine position.[18]

Though the exact mechanism of its action is not clear, it is postulated that ARDS patients have inhomogeneous distribution of alveolar collapse and that patients in the prone position appear to have more recruitment of atelectatic dorsal lung regions.

When no contraindication, prone positioning is recommended, if it is showing benefits in ventilation. Some patients may require almost continuous prone positioning to maintain adequate gas exchange during first several days of illness (Fig. 27.5). Prone positioning can be discontinued when alterations in PaO_2 observed during position changes are <10 percent, status is clearly improved, or no obvious benefit to proning has been achieved after a prolonged period [>48 hours][19]

OTHER ADJUNCTIVE THERAPIES

Inhaled Nitric Oxide

Inhaled nitric Oxide [iNO] is a selective pulmonary capillary vasodilator. Since iNO is only delivered to well ventilated parts of the lung, it improves V/Q mismatch. It may also decrease the overproduction of cytokines in patients with severe ARDS and has also been shown to attenuate increases in capillary permeability.

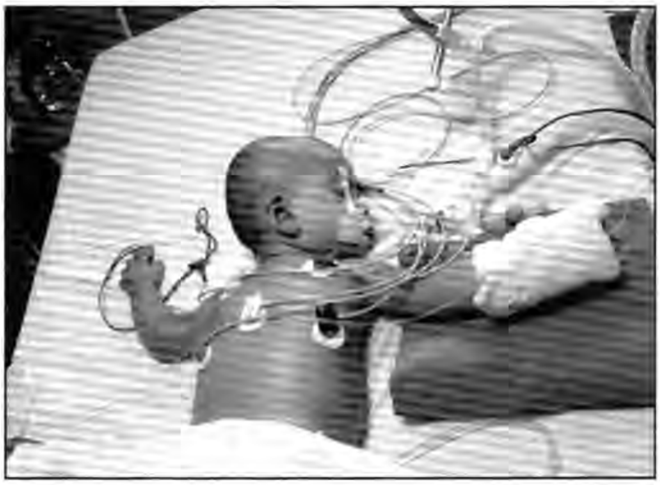


Fig. 27.5: Prone positioning *(For color version see Plate 6)*

Though the short-term beneficial effects of iNO on PaO_2 in patients of ARDS has been shown by some studies it has not been found to have significant long term effect on arterial oxygenation and on mortality.[20] Current recommendations are not in favour of using it routinely in patients with hypoxemia due to acute lung injury. However, in children with severe hypoxic respiratory failure, iNO was found to reduce the requirement for extracorporeal membrane oxygenation [ECMO].[21]

Corticosteroids

A lot of work has been done to study the role of steroids in management of ARDS, but it remains controversial.

Meduri et al reported, methylprednisolone therapy could be effective in improving lung function and outcome in patients with unresolving ARDS, if it is administered before end-stage fibrosis develops. Another observation was that methylprednisolone therapy should be prolonged to contain host defense response, which is crucial to the reversal of ARDS and multi-organ dysfunction syndrome.[22]

Recommended dose of methylprednisolone is 2 mg/kg and it should be started at an early stage [after at least 7 days of mechanical ventilation], continuing up to 32 days.[23] Above recommendations remain controversial due to conflicting studies recently.

Extracorporeal Membrane Oxygenation (ECMO)[22]

ECMO involves placing the patient on cardiopulmonary bypass to allow lungs to rest and venous blood is circulated through membrane oxygenator for oxygenation and carbon dioxide removal.

Many studies have shown that the survival increases with "early" [7 days or less of mechanical ventilation] institution of ECMO therapy, presumably when the disease remains reversible and before ventilator induced lung injury occurs. Ventilator duration for more than 10 days prior to commencing ECMO is a relative contraindication. Though there is no randomised controlled trials defining the role of ECMO in paediatric patients with ARDS or ALI, it has been suggested that "ECMO is a safe and effective means to keep patients alive during severe respiratory failure that would otherwise be fatal."[24]

Nutritional Support

Enteral nutrition instituted early in the course of ARDS is beneficial in view of high degree of catabolism especially in clinical settings of sepsis and trauma. In patients who do not tolerate enteral feeds deficiency of essential fatty acids can occur with prolonged debilitating illness requiring intralipid administration. Enteral feeds can be used as continuous feeds in small volumes in patients who are sedated and muscle relaxed as well as on inotropic support. Abdominal girth should be closely monitored with gradual advancement of feeds to a total amount equal to the patients total fluid requirement. Excessive carbohydrate diet may increase CO_2 production and worsening respiratory failure. Optimum calorie: nitrogen ratio is 150:1 to 200:1.

Fat microembolism in pulmonary capillaries in patients receiving fat emulsions has been described as a risk factor which could worsen the hypoxemia. This can be avoided if triglyceride levels are closely monitored. Liver function tests, blood urea, creatinine should be monitored twice a week particularly in patients who are receiving total parenteral nutrition.

Broad Spectrum Antibiotic Coverage

Initial therapy with a third generation cephalosporin and aminoglycoside should be considered until culture reports are available. In Indian settings infections with staphylococcus, pseudomonas and klebsiella are common; and appropriate changes in antibiotic therapy should be made based on cultures and sensitivity reports. Indiscriminate use of multiple antibiotics should be discouraged to prevent emergence of resistant organisms as well as fungal infections.

Complications

Barotrauma (pneumothorax, pneumomediastinum, bronchopleural fistula, surgical emphysema), oxygen toxicity and secondary infections are most frequently seen treatable complications. However progression to multi system organ failure carries a greater than 50 percent mortality.

Outcome and Prognosis[25-27]

ARDS *per se* carries a 45-60 percent mortality (primary ARDS due to pulmonary causes has lower mortality when compared to non pulmonary causes). Lodha et al have reported a mortality of 75 percent on a retrospective chart review on pediatric patients with ARDS. More recently mortality as low as 30 percent has been reported. This is attributed to better understanding of conventional ventilation and supportive measures. Incidence of chronic lung disease, oxygen dependence seems to be related to duration of ventilation as well as barotrauma. In authors experience duration of ventilation longer than a month tends to be associated with higher incidence of chronic lung disease, oxygen dependence, prolonged muscle weakness secondary to prolonged infusion of muscle relaxants , narcotic/ sedative withdrawal syndrome as well as nosocomial infections including systemic candidiasis. Early medical intervention (PICU admission) in hypoxemic phase should be encouraged, so that close monitoring of respiratory status and prompt initiation of ventilation can be instituted before a respiratory or cardiorespiratory arrest occurs, which carries 98 percent mortality as well as 98 percent chance of severe neurological deficit in case of survival. We have recently reported beneficial effects of low tidal volumes in Indian settings.[28]

Newhorizons: Interestingly, use of surfactant has been recently reported to significantly improve the outcome in a US study.[29] HFOV is now being used in adult patients also.

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CHAPTER

28

Empyema Thoracic in Children: A Current Perspective

Saroj Kumar Singh, Meenu Singh, Sujit Kumar Chowdhary

Pneumonias are associated with parapneumonic effusions and their incidence depends on infecting organism. A small proportion of parapneumonic effusions can progress to empyema if treatment is delayed or inadequate. Due to poor facilities for culture, delay in seeking medical opinion and indiscriminate use of antibiotics, it is very difficult to isolate microorganisms in Indian conditions. Data from India on empyema in children is scarce. There is no universally accepted guidelines for the management of empyema. We will discuss the diagnosis and management of empyema thoracic in children on the basis of evidence in medical literature.

Definition

Empyema thoracic is characterized by presence of pus or microorganism in the pleural fluid. Microorganisms may be seen on smear examination or on culture. In the absence of microorganism, the diagnosis is made if the following criteria are met: (a) The pH of pleural fluid is less than 7.0; (b) Lactic dehydrogenase (LDH) is more than 1000 IU/L, glucose is less than 40 mg/dl or lactate is more than 5 mol/L or 45 mg/ml.[1-3]

Predisposing Factors

Pneumonia is the most common predisposing condition for development of empyema. Nearly half of the patients develop empyema as a complication of pneumonia and parapneunic effusion.[4] Neglected foreign body can cause bronchiectasis and predispose to empyema.[5] Factors that predispose a patient to pulmonary infection and empyema are poor orodental hygiene, periodontal disease, mental retardation, cardiac failure, sedative drug use, cortico-steroid or immunosuppressive therapy and aspiration syndromes.[6-9] Among other factors which can be associated with empyema are Intravenous drug abuse, sub diaphragmatic infection, lung abscess, retropharyngeal abscess, abscessed mediastinal lymph nodes, para-vertebral abscess, trauma and thoracic surgery or thorcocentesis or introduction of organism during upper abdominal surgery.[7-10] Predisposing conditions unique to children include cerebral palsy, immunosuppression, congenital heart disease and prematurity.[11-13] In a small percentage of cases no predisposing factor is encountered.[9,14]

Causative Organisms (Table 28.1)

Staphylococcus aureus is the most common pathogen in pediatric age group.[15,16] *Streptococcus pneumoniae, Streptococcus pyogenes* and *Haemophilus influenzae* are other common bacteria implicated in empyema thoracic in children.[13,14] Pneumococcal pneumonia is associated with parapneumonic effusion in 40 percent patients but only 5 percent progress to empyema.[13] Group A Streptococcus is less common but it produces large pleural effusions that progress rapidly to produce empyema and sepsis.[14,17] *Pseudomonas aeruginosa* was found to be the second most common pathogen in one series.[19] Common aerobic and anaerobic organisms causing empyema are mentioned in Table 28.1.[4,7,11,13-21] Two percent

Table 28.1: Pathogens leading to empyema thoracic in children

Aerobes	Anaerobes	Miscellaneous
Staphylococcus aureus	Bacteroides species	Candida albicans
Streptococcus pneumoniae	Fusobacterium species	Aspergillus fumigatus
Haemophilus influenzae	Microaerophilic streptococci	Entamoeba histolytica
Staphylococcus epidermidis	Peptostreptococcus	
Escherichia coli	Peptococcus	
Klebsiella aerogenes	Clostridium perfrigens	
Pseudomonas aeruginosa	Catalase negative non-spore forming gram positive bacilli	
Mycobacterium tuberculosis	Veilonella parvula	
Serratia marcascens	Propionobacterium acne	
Enterobacter species		
Streptococcus milleri		
Legionella pneumophila		
Streptococcus viridans		

cases of tuberculous pleurisy can progress to tuberculous empyema.[16] It represents a chronic active infection of the pleural space that contains large number of tubercle bacilli.[19]

Anaerobes are more common after 6 years of age, Aspiration pneumonia is the most common cause for anaerobic infection followed by lung abscess, sub dia-phragmatic abscess and spreading infection from adjacent sites, e.g. periodontal, retropharyngeal, peritonsillar and neck abscesses. Anaerobes and enterobacter are common in mixed infections. Among fungi Aspergillus fumigatus and Candida albicans can cause empyema.[21] Amoebic liver abscess may burst in the pleural cavity leading to empyema.[4]

Clinical Features

Clinical signs vary depending on the type of organism isolated, age of the patient, stage of the effusion and prior antibiotic therapy.[11] A high index of suspicion and appreciation of factors that predispose to development of empyema facilitates its recognition. It is more common in infants and toddlers of poor socio-economic group. Common symptoms are chills, fever, dyspnea, chest pain or referred pain, night sweat, malaise, cough and increased sputum production.[1,4,11,20,22] Fever may not be present in immunocompromised or debilitated patients.[21,23] Pneumonia caused by aerobic pathogens has a symptom free period before progressing to empyema bacteria multiply in the pleural space during this period.[11,22]

Among signs, diminished breath sounds, dullness to percussion, pleural friction rub, bronchophony or aegophony above pleural effusion and mediastinal shift are most common. Rarely erythema, swelling, focal chest wall heat, a preference to lie on the affected side or splinting of the chest may be noticed.[4]

Pathophysiology

During first 48-72 hours parapneumonic effusions are small, sterile with pleural fluid pH more than 7.30, glucose more than 60 mg/dl, LDH less than 500 IU/L and polymorphonuclear leucocytes (PMNS) predominant exudate.[24-27] If pneumonia remains untreated, the amount of pleural fluid increases and bacteria invade pleural space.[28] Parapneumonic effusion progresses to fibrinopurulent stage characterized by an increased number of polymorphs, a fall in pleural fluid pH and glucose with an increase in the pleural fluid LDH. The pleural fluid/serum glucose ratio decreases to less than 0.5 and the absolute concentration of glucose is usually less than 40 mg/dl because of increased glycolysis due to phago-cytosis by neutrophils and bacterial metabolism.[29] Due to glucose metabolism, lactic acid and CO_2 accumulate in the pleural space leading to fall in the pH below 7.10 and glucose below 40 mg/dl while LDH level increases above 1000 IU/L Pleural fluid becomes clottable with a large concentration of plasma proteins in the pleural space and reduced fibrinolytic activity due to inflammatory injury.[30] These processes result in deposition of a dense layer of fibrin on both pleural surfaces. Fibroblasts move into the pleural space and produce septa leading to loculations. Later on fibroblasts grow in the exudate and lead to formation of the peel.[31] In simple empyema the pleural fluid is free flowing with single locule while in complex empyema pleural fluid is multi loculated.

Stages of Empyema

Pathological response in empyema thoracic is divided in three stages not sharply distinct but one stage merges into another. Progression of stages depend largely on the infecting organism.[11,31,32]

a. *Exudative stage (1-3 days)* This is the immediate res-ponse with outpouring of the fluid. During this stage the fluid is thin and considered as simple parapneumonic effusion. Pleurall fluid analysis shows pH more than 7.30, glucose more than 60 mg/dl, pleural fluid/serum glucose ratio more than 0.5, LDH less than 1000 IU/L, low cellular content while Gram stain and culture is negative for micro-organism.
b. *Fibrino purulent stage (4 to 14 days)* This stage is characterized by large number of poly-morphonuclear leukocytes and accumulation of fibrin in the effusion. Pleural fluid pH and glucose level fall while LDH level increases. Effusion become purulent and there is tendency towards formation of loculations. Gram stain and culture of the pleural fluid is positive for micro-organism. Pleural fluid may be purulent or have pH <7.10, glucose <40mg/dl and LDH >1000IU/L.
c. *Organizing stage (after 14 days)* During this stage fibroblasts grows into exudate leading to formation of an inelastic membrane "the peel". Thickened pleural peel may prevent the entry of anti-microbial drugs in the pleural space and in some cases can lead to drug resistance. A thickened pleural peel can restrict the lung movement leading to "trapped lung". This complication is most common with Staphylococcal empyema.

Investigations

Hematological Investigations

Hematological findings are non-specific. Leukocytosis with polymorphonuclear cells predominance is most common finding but leukopenia has been observed rarely in severely ill patients and in those having organ transplant.[12,22] In critically ill patients anemia, abnormal liver function and hypoalbuminemia suggest poor prognosis.[1,12]

Radiological Investigations

Chest X-ray

Chest radiography is the first line investigation for patients with pleural disease.[33] Large pleural effusions can be diagnosed in posteroanterior (PA) view.[13] In adults more than 200 ml of fluid is needed to broaden costophrenic angle and 500 ml fluid obscures the hemidiaphragm in PA view.[12] Lateral decubitus view with affected side inferior facilitate recognition of smaller volumes of fluid. Postural changes help in recognition of loculations.[16]

Chest Ultrasound

Ultrasonography (USG) chest is a useful modality for diagnosis of empyema and due to freedom from radiation it is a better choice than X-ray for follow up. Ultrasound guided thoracocentesis and catheter placement has better success rate with fewer complications. Sonographic appearance of pleural fluid ranges from an anechoic (completely echofree or sonolucent) to very echogenic. Transudates are usually anechoic, whereas exudates can be echoic or anechoic.[34] Sonography can distinguish solid from liquid pleural abnormalities with 92 percent accuracy compared to 68 percent accuracy with chest X-ray. Combined use of both modalities increases accuracy up to 98 percent.[35] USG may help in diagnosing empyema by demonstrating limiting membranes suggestive of the loculations even if they are invisible on CT scan. Sonography can be used to determine nature of effusion which can be anechoic, homogenously echogenic, complex non-septated and complex septated.

Computed Tomography

In CT scan chest empyema appears well defined, smooth, round or elliptical. Inflamed visceral and parietal pleura often have a markedly thickened appearance interposed empyema fluid between parietal and visceral pleura give rise to "split pleura sign" of empyema.[36] CT scan can differentiate extra pleural and subcostal fat external to thickened pleura by its much lower CT attenuation. It also helps in differentiating empyema from consolidation and lung abscess. Use of intravenous contrast causes enhancement of pleural membranes and should be given for optimum evaluation of pleuro-pulmonary diseases.[36] In tuberculous empyema CT scan show a thick calcific ring and thickened ribs surrounding loculated pleural fluid.[19]

Thoracocentesis and Pleural Fluid Analysis

In patients with pneumonia, pleural effusion should be ruled out by X-ray chest including a lateral decubitus view with affected side inferiorly. If measurement of effusion from inner margin of chest wall up to upper level of fluid in lateral decubitus view is greater than one centimeter, immediate diagnostic thoracocentesis should be done.[37] The site for thoracocentesis is 1 cm below the upper level of dullness because inflammed pleura may lead to upward displacement of solid organs lying below diaphragm.[16] The characteristic of the fluid including odor must be noted. Gram stain, culture, pH, glucose, LDH and WBC count are performed on the aspirate. Pleural fluid for pH must be handled meticulously like arterial blood for pH and drawn anaerobically into a syringe with 0.2 percent of 1:1000 heparin and placed on an ice until analyzed. In the tube for glucose estimation, 2 ml of pleural fluid is collected. An anti glycolytic substance fluoride oxalate 0.1 ml (containing 2 mg of sodium fluoride and 6 mg of potassium oxalate) must be added in it to prevent *in vitro* glycolysis due to the polymorphs.[38] Uncomplicated parapneumonic effusion has pH more than 7.30, glucose more than 60 mg/dl and LDH less than 1000 IU/L (mostly less than 500 IU/L). Complicated parapneumonic effusion is characterized by pH less than 7.10, glucose less than 40 mg/dl and LDH more than 1000 IU/L. In the presence of acidosis in the blood gas, pleural fluid acidosis is defined as pH at least 0.15 unit below blood pH Pleural fluid pH value 0.3 unit less than blood pH value may need chest tube insertion.[38] Two third of the cases of anaerobic infection have malodorous empyema.[39,40] Protein level and specific gravity is not helpful in diagnosis and therapy of empyema.[4] Tuberculous empyema can be confirmed by stains for acid fast bacilli in fewer than 25 percent cases but pleural biopsy and culture can diagnose more than 90 percent cases.[41] Pleural fluid adenosine deaminase levels more than 70 U/L supports the diagnosis of tuberculous empyema. Diagnostic utility of polymerase chain reaction (PCR) for detection of mycobacterial antigen in pleural fluid is still under investigation.[4]

Chylous effusion can be excluded by testing the fluid for neutral fat, pH and sedimentation values after centrifugation at 5000 g. Purulent empyema has acid pH and cell fragments will sediment where a chylous effusion will have a neutral pH and remain opaque after centrifugation.[4]

Treatment

Appropriate antibiotics and drainage of pus allows complete recovery in the cases of empyema thoracic. Table 28.2 shows a treatment plan based on Light's classification.[40] This is based on the amount of fluid present, biochemical characteristics, the result of Gram stain and cultures and presence or absence of loculations.[11,38,42]

Antimicrobial Therapy

Appropriate antibiotic therapy should be started in all cases of parapneumonic effusion and empyema on the basis of suspected etiological agent and should be changed later on the basis of culture and sensitivity report. Antibiotics used against common pathogens leading to empyema are given in Table 28.3.[16,43] Since S. aureus, S. pneumoniae and H. influenze are most common pathogens. Injection Cloxacillin along with injection Cefotaxime or injection Ceftriaxone can be used for initial therapy. If anaerobic infection is strongly suspected, injection Clindamycin should be added. Due to synergistic effect Aminoglycosides can be added in suspected *S. aureus* infection or Ciprofloxacin can be substituted for aminoglycosides.[4] Due to poor activity in the pus monotherapy with aminoglycosides should not be used. Amoxicillin combined with β-lactamase inhibitor such as clavalunic acid can be used at a dose based on amoxycillin component of 40-80 mg/kg in *S. aureus* and *H. influenzae* infection.[42,44] In methicillin resistant S. aureus infection intravenous Vancomycin 60 mg/kg/day in four divided dosage is the drug of choice. Penicillin G is drug of choice for penicillin susceptible pneumococci. Pneumococci with intermediate susceptibility to penicillin should

Table 28.2: Light's classification and treatment plan for various stages of parapneumonic effusions and empyema

Class of parapneumonic effusion	Radiological, Biochemical and Microbiological characteristics	Treatment
Class 1 Nonsignificant parapneumonic effusion	Small < 10 mm thick on lateral decubitus X-ray	No thoracocentesis needed Antibiotics alone
Class 2 Typical parapneumonic Effusion	> 10 mm thick Glucose > 40 g/dl, pH>7.20 Gram stain and culture negative	Antibiotics alone No tube thoracostomy
Class 3 Borderline complicated Parapneumonic effusion	pH < 7.00 and/or LDH>1000 and Glucose > 40 mg/dl Gram stain and culture negative	Antibiotics + serial thoracocentesis! tube thoracostomy
Class 4 Simple complicated Parapneumonic effusion	pH <7.00 and/or Glucose <40 mg/dl and/or gram stain and culture positive Not loculated not frank pus	Antibiotics + serial thoracostomy but if above measures fail then decortication
Class 5 Complex complicated Parapneumonic effusion	pH < 7.00 and/or glucose < 40 mg/dl and/or Gram stain and culture positive Multiloculated not frank pus	Same as class 4 + Thrombolytics or adhesionolysis by VATS/Thoracoscope debridement if above measures fail then decortication
Class 6 Simple empyema	Frank pus present, Single locule with free flowing pus	Same as class 4
Class 7 Complex empyema	Frank pus present Multiple locules	Same as class 5

Table 28.3: Guidelines to antimicrobial therapy of parapneumonic effusion and empyema

Infecting agent		Drugs	Drug dosage (mg per kg per day)	Duration
Aerobic bacteria				
Staphylococci	a.	Cloxacillin	100 to 200 mg in 3-6 doses IV initially	3-4 weeks
	b.	Methicillin	200 to 400 mg in 3-4 divided dosage IV initially	3-4 weeks
Haemophilus influenzae	a.	Cefotaxime	150-225 mg in 3 doses IV	7-14 days
	b.	Ceftriaxone	80-100 mg in 1-2 doses	
	c.	Chloramphenicol	50-100 mg in 4 doses	
Pneumococci and Streptococci		Penicillin G	100,000-400,000 units in 4-6 doses	7-14 days
Escherichia coli and Klebsiella		Cefotaxime	150-225 mg in 3 doses IV	14 days or longer
Pseudomonas aeruginosa	a.	Ticarcillin	200-300 in 4-6 doses or IV	10 days or longer
	b.	Ceftazidime	125-150 in 3 doses with IV	
	c.	Tobramycin	5-7 mg in 3 doses IV	
Anerobic bacteria				
B. Fragilis		Clindamycin	20-40 mg in 3-4 doses IV	6-12 weeks
All except B. fragilis	a.	Clindamycin	20-40 mg in 3-4 doses IV	6-12 weeks
	b.	Penicillin G	100,000-400,000 units in 4-6 doses IV	

be treated with Cefotaxime or Ceftriaxone. *S. pneumoniae* with high level of resistance to pencillin (MIC >2 µg/ml) and to ceftriaxone or cefotaxime (MIC >4 mg/ml) should be treated witl Vancomycin.[5] Parenteral Cefuroxime o Chloramphenicol can be used against *S. pneumonia* and *H. influenzae*.[45] Resistance to extended spectrum cephalosporins such as Cefotaxime or Ceftriaxone is not reported in *H. influenzae* infection.[44] All these antibiotics attain many fold higher concentration in pleural fluid than minimum inhibitory concentration (MIC). Children can remain febrile for 10-14 days in S. aureus infection and 7 or more days in *S. pneumoniae* and *H. influenzae* infection despite adequate antibiotic therapy.[45] Parenteral therapy should be continued for 48-72 hours after patient become afebrile followed by oral therapy to complete the course.[45] Antibiotic should be continued until patient is afebrile, WBC count is normal, tube thoracostomy yield is less than 50 ml of fluid per day and radiograph show considerable clearing.[46] Normally *H. influenzae* and *S. pneumoniae* need 7-14 days course of antibiotics while *S. aureus* needs 3-4 weeks. In anaerobic empyema duration of therapy is variable. Often 6-12 weeks course is required before the lung lesions is cleared or only a small stable residual disease is left.[16]

In suspected cases of multi drug resistant tuberculous empyema, treatment should be started with five drug combination of Isoniazid (H), Rifampicin (H), Pyrazinamide (Z), Ethambutol (E), Streptomycin (S) {sometimes added Thiacetazone} for first 2 months followed by another month of four drug therapy (HRZE).This is followed by three drug therapy (HRE) for 5 to 6 months. If the sputum is positive for mycobacteria at the end of four months second line drug therapy is considered.[47] Once culture report is available, individualized regimes based on antimicrobial susceptibility with two or more effective drugs should be given.[4] Tuberculous empyema presents a special situation. Like all tuberculous effusions steroids may help to reduce effusion and its sequelae, however our institutional practice is not to use corticosteroids because of the large number of mycobacteria present in the empyema fluid.

Empyema Drainage

Empyema drainage is an important component of empyema treatment. A chest tube with an under water seal should be placed if pleural fluid has any of the following characteristics as frank pus, smear positive for microorganisms or biochemical analysis showing pH less than 7.10, glucose less than 40 mg/dl and LDH more than 1000 IU/L.[16] Repeated thoracocentesis is rarely successful in such cases. Small-bore percutaneous catheters can be used if the fluid is thin. Drainage under direct CT guidance is most successful if empyema collection is small.[48] Chest tube drainage is advised for drainage of tuberculous empyema. Chest tube must be kept inside till drainage is less than 30-50 ml per day and cavity size is less than 50 ml.[16,28]

Thrombolytic Therapy

Thrombolytic therapy can be used in multiloculated empyema. Multiloculation of empyema is defined on the basis of USG/CT finding showing presence of two or more loculations that are separated and without communication.[49] Loculations are defined by one or more of the following criteria-failure of effusion to layer on decubitus film, fixed fluid in abnormal locations, septations seen on USG or CT scan (present prior to instrumentation). Streptokinase (SK) and Urokinase (UK) are used as thrombolytics. SK is a non-enzymatic streptococcal exotoxin. It becomes plasmin activator after combining with plasminogen. When inactive plasminogen is cleaved, plasmin is generated. Plasmin hydrolyse fibrin leading to hydrolysis of fibrin coagulum. UK is a direct plasminogen activator. For one molecule of UK, one molecule of plasmin is produced and thus making it more effective.[49]

SK 2,50,000 unit or UK 1,00,000 unit in 100 ml normal saline was instilled through chest tube and tube was clamped for 3 to 6 hours. Instillation are done daily till minimum amount of fluid is left and no fluid comes on instillation.[6-9] In one series number of instillation in two randomly assigned groups for SK and UK were 6 ± 2.16 and 5.92 ± 2.05, respectively and increase in total net volume of fluid drained was comparable in both groups.[7] Transient increase of body temperature was noted in 28 percent cases of SK while no complication was noted with UK. In one series UK as little as 50,000 unit per instillation was found to be successful in 95 percent cases.[8] In India cost of SK 7,50,000 unit is Rs. 1400 and unused amount can be stored in the refrigerator for 24 hours. UK 250,000 units cost Rs 1865 (Win-Medicare company).

Surgical Modalities of Treatment

Videoassisted Thoracoscopic Surgery (VATS)

VATS is quite effective in lysis of adhesions and removal of fibrinous material from the pleural cavity in multiloculated empyema. When necessary, a limited decortication of fibrinous material can be done using a standard or endosurgical instruments.[50,51] It also helps in visualization and breakdown of deeper pockets and putting the drainage catheter at appropriate site.[50] If significant fibrosis or entrapment is found during VATS exploration, thoracostomy is performed. The VATS instrument helps in identifying most appropriate site for thoracostomy incision. In organizing stage VATS is often not useful.

Thoracoscopic Debridement and Irrigation

In multiloculated empyema its efficacy is comparable to thrombolytics. It helps by breaking adhesions and converting the multi-loculated cavity into a single cavity. Success rate is as high as 69 to 89 percent.[52,53] Formal decortication is reserved for cases with fibrotic visceral peel that restricts the expansion of underlying lung.[54]

Decortication

It is advised for the cases not helped by above procedures. Some studies advocate early decortication to avoid permanent surgical impairment.[1,12,20] If patient is too debilitated to tolerate thoracostomy, then open drainage is preferable.[28]

Bronchopleural Fistula

Spontaneous healing of bronchopleural fistula is extremely rare. Very few cases may heal after closed tube drainage of thoracic cavity. If this fails to happen in 2-3 weeks time, decortication with excision of the fibrous encasement of the lung is indicated. This results in expansion of lung with closure of obvious fistula in few cases. Persistence of bronchopleural fistula because of inability to suture, or sutures giving way is treated with long-term external drainage after two weeks of surgery with gradual withdrawal of the chest tube. This may allow the fistula to close over a period of up to one-year. If all these interventions fail, then one is left with the option of thoracoplasty or resectional surgery of the lung parenchyma (lobar resection). These are formidable procedures in children and should not be undertaken without adequate conservative management and experience. The response to all these attempts depends on the size of fistula, state of underlying lung and contralateral lung, presence or absence of systemic illness, nutritional rehabilitation and medical measures.[55]

Effect on Pulmonary Function Test

Pulmonary function is found to be normal in most of the cases.[56] A positive correlation between age and recovery period has been reported. Younger children fared less well.[18] Mild obstruction has been documented on pulmonary function testing in few patients in one series and its rate was similar in cases who underwent chest tube drainage and those who did not.[57] Few cases show complications such as scoliosis, mild pleural thickening and mild restrictive defect.[54]

SUMMARY (FLOW CHART 28.1)

Empyema thoracic is a common complication o pneumonia. Children of poor socio-economic statu and below 3 years of age are most commonly affected Staphylococcus aureus is the most common causativ organism. A high index of suspicion helps i diagnosis. X-ray chest, USG chest and CT scan ar most useful modalities for diagnosis and follow-up Thoracentesis and pleural fluid analysis help i deciding therapy. Proper antibiotic coverage an chest tube drainage is most important step in th management of empyema. Thrombolytics such a Streptokinase and Urokinase, or Video assiste thoracoscopic surgery or thoracoscopy with debride ment are effective for multi-loculated empyem Cases not responding to above measures nee decortication. Long term follow up shows norm pulmonary function test in majority of the cases.

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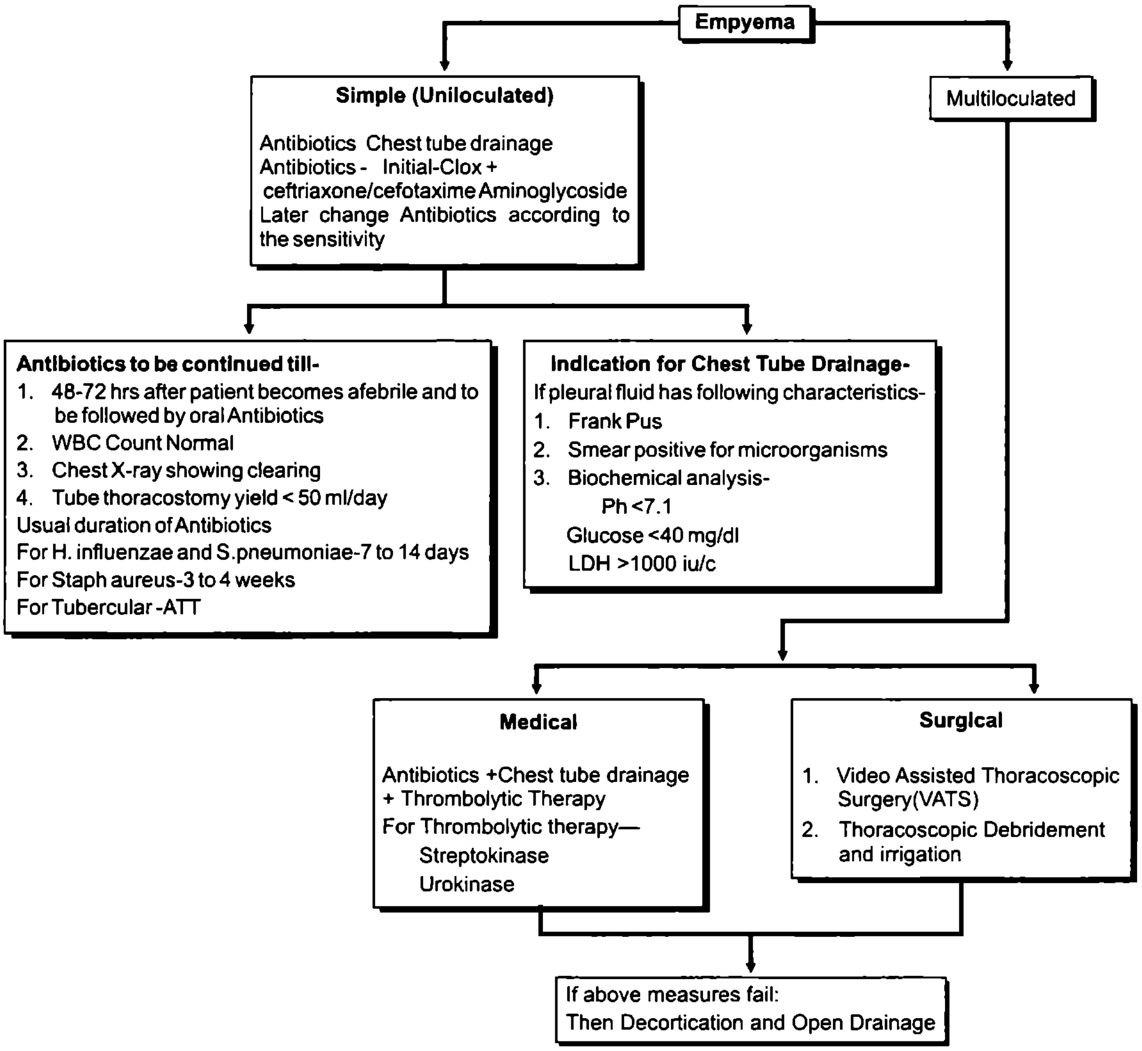
Flow chart 28.1: Empyema


Empyema
Simple (Uniloculated)
Antibiotics Chest tube drainage
Antibiotics - Initial-Clox + ceftriaxone/cefotaxime Aminoglycoside
Later change Antibiotics according to the sensitivity
Multiloculated
Antibiotics to be continued till-
1. 48-72 hrs after patient becomes afebrile and to be followed by oral Antibiotics
2. WBC Count Normal
3. Chest X-ray showing clearing
4. Tube thoracostomy yield < 50 ml/day
Usual duration of Antibiotics
For H. influenzae and S.pneumoniae-7 to 14 days
For Staph aureus-3 to 4 weeks
For Tubercular -ATT
Indication for Chest Tube Drainage-
If pleural fluid has following characteristics-
1. Frank Pus
2. Smear positive for microorganisms
3. Biochemical analysis-
Ph <7.1
Glucose <40 mg/dl
LDH >1000 iu/c
Medical
Antibiotics +Chest tube drainage + Thrombolytic Therapy
For Thrombolytic therapy—
Streptokinase
Urokinase
Surgical
1. Video Assisted Thoracoscopic Surgery(VATS)
2. Thoracoscopic Debridement and irrigation
If above measures fail:
Then Decortication and Open Drainage

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CHAPTER

Air Leak Syndromes

Utkarsh Kohli, Rakesh Lodha

PNEUMOTHORAX

Pneumothorax is defined as abnormal accumulation of air within the pleural cavity. Based on their etiology, pneumothoraces can be classified as, open, closed and spontaneous (Table 29.1). Closed pneumothorax arises when air enters the pleural cavity by disruption of pulmonary parenchyma. Traditionally, positive pressure mechanical ventilation, airway obstruction due to foreign body, bronchial asthma, pulmonary infections, acute respiratory distress syndrome (ARDS) and acute lung injury due to inhaled physical and chemical agents are considered important risk factors for closed pneumothorax.[1] However, recent evidence shows that, in patients with sepsis-induced acute respiratory distress syndrome, who were receiving mechanical ventilation with conventional pressures and volumes, there were no significant correlations between high ventilatory pressures or volumes and the development of pneumothorax or other air leaks, and pneumothorax or other air leaks were not associated with a significantly increased mortality rate.[2] Invasive diagnostic procedures involving thoracic and abdominal organs also increase the risk of pneumothorax. Open pneumothorax arises due to disruption in the integrity of chest wall and parietal pleura. Major causative factors for open pneumothorax are penetrating chest trauma and invasive diagnostic and therapeutic procedure involving chest wall and pleura. Primary spontaneous pneumothorax is a distinct entity which, by definition, occurs in absence of lung disease, and is more frequently seen in young, lanky and asthenic males. Cigarette smoking is an important risk factor for spontaneous pneumothorax. Subpleural blebs are more frequent in these patients, and rupture of these blebs, possibly related to sudden changes in intrathoracic pressure during episodes of coughing or spells of bronchospasm, leads to pneumothorax. Positive intrathoracic pressure associated with labour and delivery is also known to be associated with spontaneous pneumothorax in healthy women. This entity is known as Hamman's syndrome. Primary spontaneous pneumothorax recurs in approximately 30% of the cases.[1,3]

Table 29.1: Causes of pneumothorax

Closed pneumothorax

1. Pulmonary disease
   Foreign body.
   ARDS
   Respiratory infections (Measels, P carinii, Staphylococcus, Tuberculosis)
   Bronchial asthma.
   Chemical pneumonitis.
   Tumors.
2. Iatrogenic
   Mechanical ventilation.
   Central venous catheterization.

Open Pneumothroax
Invasive pleural and pulmonary procedures.
Chest trauma. Laproscopic procedures.

Spontaneous Pneumothorax
Idiopathic.
Familial.
Hamman's syndrome.

Pneumothorax commonly manifests as sudden onset severe chest pain accompanied by tachypnea, tachycardia, dyspnea and cyanosis. The intensity of symptoms varies with the severity of air leak, the time interval over which the leak occurred and severity of underlying lung disease. Character and exact site of pain are variablung disease. Some patients may report minimal substernal discomfort, while others present with frank pleuritic chest pain. Younger children may just manifest with sudden onset respiratory distress or worsening of distress. On examination, jugular venous pressure is elevated and the chest movement is decreased on the involved side. Percussion note is hyper-resonant but tactile vocal fremitus, vocal resonance and air entry are all reduced on the same side. If the air is under pressure, there is shift of trachea and mediastinum towards the opposite side; this is called a tension pneumothorax and it is a medical emergency.[1]

The most important investigation to confirm the diagnosis of pneumothorax is chest radiography (Figs 29.1 and 29.2). Presence of a hyperlucent area on erect postero-anterior chest radiograph, with absent lung markings and a distinct visceral pleural border, which is not normally seen, are essential to make a diagnosis of pneumothorax. Bedside methods to confirm the diagnosis include transillumination of chest wall with cold light and aspiration of pleural space with a fluid filled needle. An arterial blood gas analysis can help in determining the degree of respiratory compromise caused by pneumothorax and usually shows hypoxemia and hypercarbia.[1]

Treatment of pneumothorax depends upon the severity of symptoms experienced by the patient. Small minimally symptomatic pneumothoraces (involving less than 15% of hemithorax) can be left to resolve on their own and these patients can be managed at home after initial observation of 6 hours in the hospital. This process can be hastened by making the patient breathe 100% oxygen. All significant pneumothoraces require evacuation of air from the pleural space. This can be done by inserting a thoracotomy tube under local anaesthesia and applying suction. Tube should be put under a water seal and should stay in place until no more air can be aspirated. In case of dire emergency, air can be evacuated from the pleural space with the help of a needle, three way connector and a water filled syringe. Chest tube placement can lead to complications like pain, hemorrhage, trauma to thoracic or abdominal viscera and, pulmonary edema if the underlying lung expands too quickly. Continuous air leak is a sign of disruption of pleural surface or communication of an airway with the pleural space (bronchopleural fistula). Continuous air leak for more than 1 week requires surgical intervention, either sewing or stapling of pleural surfaces or endoscopic instillation of sclerosants. Bronchopleural fistula can be repaired endoscopically.[1,3] Surgical intervention, to prevent recurrence, is indicated after second episode of primary spontaneous pneumo-

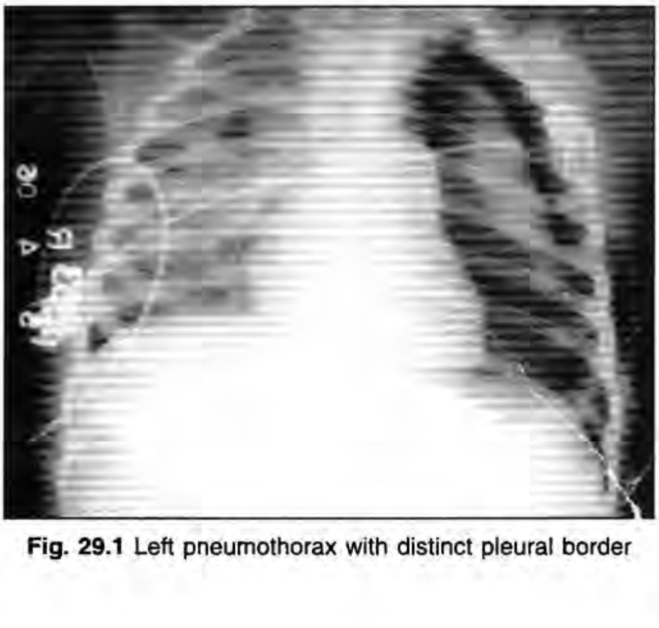

Fig. 29.1 Left pneumothorax with distinct pleural border

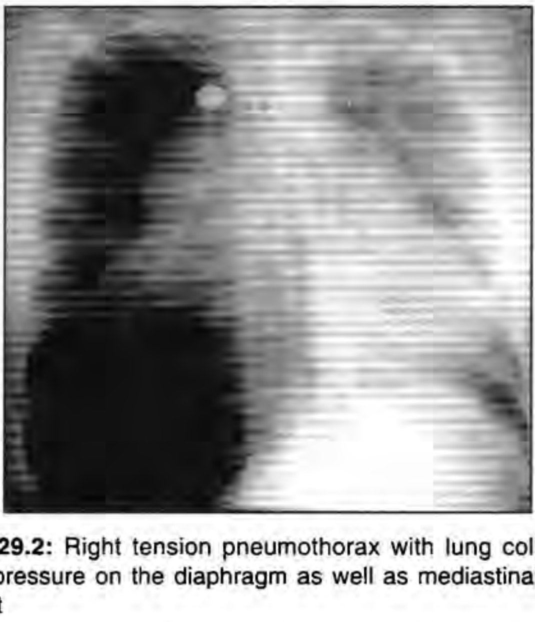

Fig. 29.2: Right tension pneumothorax with lung collapse and pressure on the diaphragm as well as mediastinal shift to left

thorax. The available methods include video assisted thoracoscopic resection of bullae through multiple chest ports, thoracoscopic resection through a single chest port and thoracotomy. All these procedures are accompanied by either mechanical pleural abrasion or insufflation of sclerosant like talc into the pleural space.[3]

Some people report substernal discomfort while others experience frank pleuritic chest pain.

PULMONARY INTERSTITIAL EMPHYSEMA

Pulmonary interstitial emphysema (PIE) is characterized by presence of air in pulmonary interstitial tissue. This complication is usually seen in sick mechanically ventilated preterm babies with significant lung disease. However, there are case reports that describe PIE in spontaneously breathing term and preterm babies.[4,5,6] PIE has also been described in asthamatics and adult respiratory distress syndrome patients.[7,8] Interstitial air can either be localized to a portion of lung, or it can spread to involve both the lungs. Interstitial air can also track along the lymphatics and blood vessels towards pleural surface and hilum and cause pneumothorax and pneumomediastinum, respectively.[9] Pulmonary interstitial air can alter pulmonary compliance, cause ventilation perfusion mismatch and can also compromise lymphatic and pulmonary blood flow.[10] PIE is also a well known predisposing factor for chronic lung disease (CLD), particularly CLD type 2, which is characterized by cystic changes.[11] Most often PIE is a transient phenomenon, but rarely it may persist and expand to form a radiolucent mass that can cause mass effect and respiratory distress. This complication is known as persistent PIE. Extreme low birth weight (ELBW) infants with PIE have been found to have lower 1 and 5 min Apgar scores, increased surfactant utilization, higher maximum inspired oxygen concentration and mean airway pressure administration during the first week of life, and increased neonatal mortality. There is also evidence to indicate that antenatal $MgSO_4$ administration is an independent risk factor for PIE in ELBW infants.[12]

Pulmonary interstitial emphysema can manifest as hypoxemia, hypercapnia, increasing ventilatory requirements in a ventilated child, hypotension and acidosis. Chest radiography reveals two distinct patterns: cysts and linear lucencies which radiate from the lung hilum.[10] Persistent pulmonary interstitial emphysema has a characteristic computerized tomographic appearance of line-and-dot in a radiolucent space. This finding is attributed to gas in the pulmonary interstitial space surrounding the bronchovascular bundles. The bronchovascular bundles then appear as linear or punctuate soft-tissue densities within the cystic radiolucencies.[13]

Main aim of the treatment is to lower the mean airway pressure by reducing PIP, PEEP or inspiratory time. Many centres use high frequency ventilation for this indication.[14] There is rudimentary evidence that indicates that 3 day dexamethasone course (0.5 mg/kg/day) is effective in either resolving or improving PIE in preterm babies upto 30 wks gestational age.[15] The infants at highest risk for death due to PIE include those with birth weight less than 1,500 g (95% of all mortalities), and those that developed pulmonary interstitial emphysema within the first 24 hours of life.[16] Severe localized PIE that fails to improve with conservative management requires either collapse of affected lung[17,18] or surgical resection of affected segment or lobes.[19,10] Initial management of persistent pulmonary interstitial emphysema should be conservative. Non-surgical maneuvers that have been effective in treating persistent PIE include high frequency ventilation, selective intubation of contralateral bronchus and decubitus positioning of the patient. Failure to respond to conservative treatment is an indication for surgical therapy.[20]

PNEUMOMEDIASTINUM

Pneumomediastinum commonly arises as a consequence of pulmonary interstitial emphysema.[21] Primary spontaneous pneumomediastinum occurs in absence of any identified risk factors while secondary pneumomediastinum is related to lung disease, invasive procedures, or a ruptured viscus. Physical examination reveals crunching noises synchronous with heartbeat, that are often accentuated during expiration (Hamman's sign). Radiological signs of pneumomediastinum depend upon air outlining various mediastinal structures and hence it appears as a thin radiolucenct line that

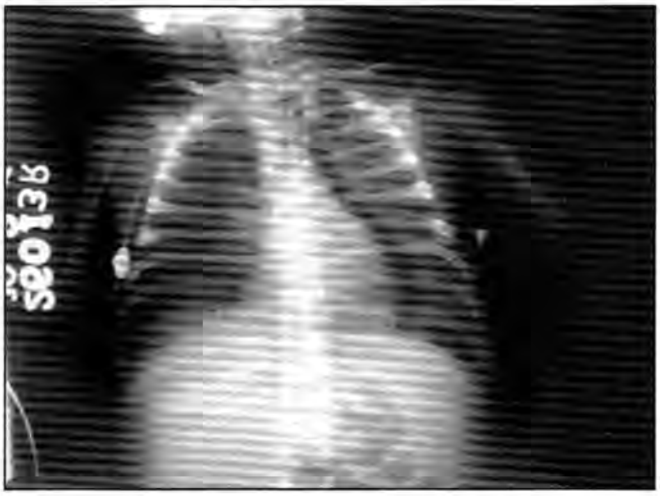
Fig. 29.3: Left pneumomediastinum

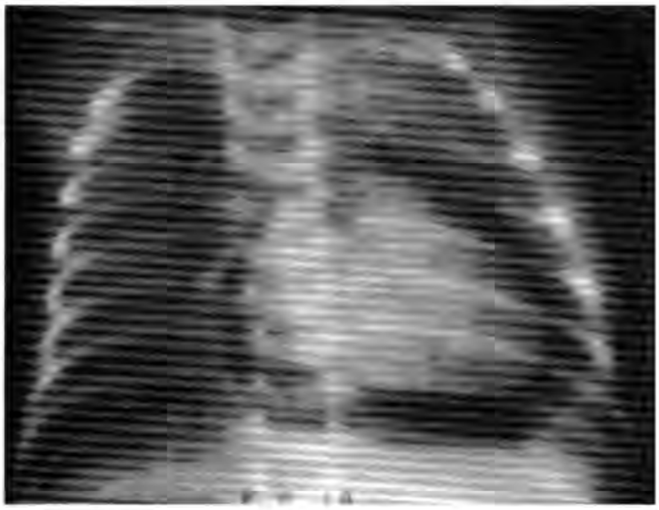
Fig. 29.4: Pneumopericardium

outlines the cardiac silhouette (Fig. 29.3), and thin, lucent, vertically oriented streaks of air within the mediastinum. Air most easily is detected retrosternally on the lateral chest radiograph while antero-posterior film may miss significant number of cases.[22] Chest radiography also reveals collection of air around the thymus gland, known as 'spinnaker's sail sign'.[23] There is evidence that shows that approximately 30% patients are missed on chest radiography and these can be diagnosed by chest CT.[24] Mediastinal air decompresses by dissecting along the subcutaneous planes of neck to cause subcutaneous emphysema, along the retropharyngeal space to cause localized collection and into the retroperitoneum. The underlying risk factors for pneumomediastinum also predispose the patient to other forms of air leaks, which should be carefully looked for. This is usually an asymptomatic condition and resolves on its own but rarely, mediastinotomy and drainage may be required if mediastinal air cannot drain and mediastinal pressure increases to such high levels that cardiac output is impaired.[10]

PNEUMOPERICARDIUM (FIG. 29.4)

This is another rare form of air leak that is frequently accompanied by other air leaks. It is frequently asymptomatic, and an incidental finding on chest radiographs. However, in critically sick patients, it carries a high fatality rate. Several common causes for pneumopericardium have have been described in literature. These include (1) trauma secondary to perforation of the pericardium by a foreign body,[25] (2) infectious-secondary to gas-producing bacilli in the pericardial fluid,[26] (3) fistula formation-secondary to perforation of a neighboring viscus such as esophagus, stomach, liver abscess or bronchus,[27-31] (4) iatrogenic- secondary to pericardiectomy,[32] assisted positive pressure ventilation in neonates[33,34] esophagostomy[35] and rarely, (5) spontaneous without any predisposing factors.[36]

Possibility of pneumopericardium must be considered in all critically sick patients with acute hemodynamic compromise. Cardiac auscultation may reveal distant heart sounds, bubbling or cracking sounds synchronous with heartbeat and a pericardial knock. Chest radiographs show heart surrounded by air, and air under the inferior surface of heart is diagnostic of this condition. Transillumination with cold light may reveal flickering of cold light with each heartbeat and an ECG shows decreased QRS voltages.[37]

Asymptomatic children with pneumopericardium should be managed conservatively. Pneumopericardium presenting with acute hemodynamic compromise should be immediately treated with needle evacuation of air through subxiphoid approach (Fig. 29.5). A pericardial tube can also be inserted for continuous drainage of pneumopericardium under echocardiographic guidance.[10]

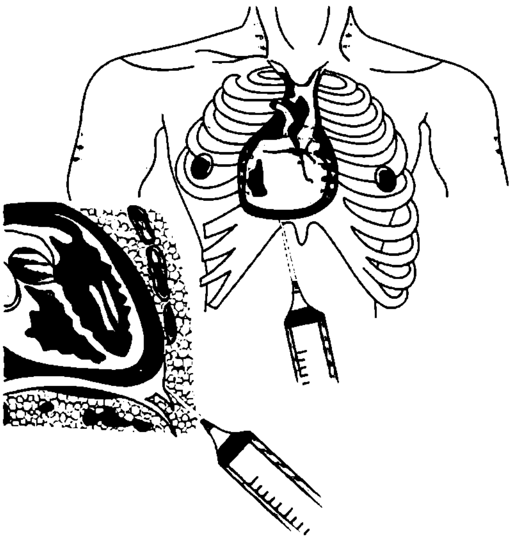

Fig. 29.5: Pericardiocentesis

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CHAPTER

Cystic Fibrosis: Clinical Manifestations and Treatment

Shushil Kabra, Madhulika Kabra, Rakesh Lodha

Cystic fibrosis (CF) is the most common life limiting recessive genetic disorder in Caucasians with an incidence of approximately 1 in 2500 children born in the United Kingdom. It is less common in African Americans (1 in 15,000) and in Asian Americans (1:31000).[1] *It also affects other ethnic groups such as black population with an incidence of 1 in 17,000 and the native American population with an approximate incidence of 1 in 80,000.*[2,3]

CF was thought to be extremely rare in India. However, a recent review of CF in Indian children suggest that CF does occur in Indian children and frequency is unknown.[4] The incidence in migrant Indian populations in the USA has been estimated to be 1 in 40000,[5] Same in UK has been estimated between 1 in 10000 to 12000.[6,7] The precise incidence of CF among Indians is unknown. As a result of the widespread belief that CF does not occur in Indians, the disease is rarely suspected and even if it is suspected the diagnosis is not confirmed due to the poor availability of facilities for diagnosis. The median age of diagnosis among Indian Americans is 12 months compared with 6 months among Caucasian American children and reflects a low index of suspicion for the disease even among Indians in western countries.[5] Reports suggest that the diagnosis of CF is delayed in Indian children resulting in severe malnutrition. It has been observed that severe malnutrition at the time of diagnosis of CF is one of the bad prognostic indicators for survival.[8]

Molecular Genetics of Cystic Fibrosis

The basic defect in CF is a mutation in the gene for chloride conductance channel, i.e. cystic fibrosis transmembrane conductance regulator (CFTR). The failure of chloride conductance by epithelial cells leads to dehydration of secretions that are too viscid and difficult to clear.

Till now more than 1000 mutations in the gene have been recognized (www.genet.sickkids.on.ca). The commonest mutation is delta F 508 which constitutes about 70 percent of the total cases.[9] The frequency of this mutation in Indian children has been reported between 19 to 44 percent.[5,10-12] From other countries in Asia it has been reported that the proportion of children with delta F 508 mutations is less than that in Caucasian population.[13]

Clinical Manifestations

The clinical features of CF are variable. The clinical features depend on age of diagnosis, supportive care received and treatment. The common clinical presentation includes meconium ileus in neonatal period, recurrent bronchiolitis in infancy and early childhood, recurrent lower respiratory tract infections, chronic lung disease, bronchiectasis, steatorrhoea and with increasing age pancreatitis, and azoospermia.[14] Pancreatic insufficiency is present in > 85 percent of CF patients (Table 30.1).

In review of 120 cases of CF at All India Institute of Medical Sciences (unpublished) showed that consanguinity was present in 15 percent. History of definite CF in family was present in 2 (2%). History suggestive of CF was present in 41 (34%) patients. Average age at diagnosis was 54 months and age of onset of symptoms was 11 months (median age of onset of symptoms was 3 months). CF affected both sexes. Common clinical features at time of diagnosis included recurrent or persistent pneumonia (98%),

Table 30.1: Common clinical features of cystic fibrosis

0-2 years	%
Meconium ileus	10–15
Obstructive jaundice	
Hypoproteinemia/anemia	
Bleeding diathesis	
Heat prostration/hyponatremia	
FTT (Failure to thrive)	
Steatorrhoea	85
Rectal prolapse	20
Bronchitis/Bronchiolitis	
Staphylococcal pneumonia	
2-12 years	
Malabsorption	85
Recurrent pneumonia	60
Nasal polyposis	6–36
Intussusception	1–05
>13 years	
Chronic pulmonary disease	70
Clubbing	
Abnormal GTT (Glucose tolerance)	20–30
DM (Diabetes mellitus)	7
Chronic intestinal obstruction	10–20
Focal biliary cirrhosis	
Portal hypertension	25
Gallstones	4–14
Azoospermia	98%

failure to thrive (90%), malabsorption (80%), rectal prolapse (13%), history of dehydration in past (13%), history of meconium ileus (8%), vitamin A deficiency (Bitot's spots) in 10 (8%), vitamin D deficiency (rickets) in 8 (6%), clubbing in 80 (67%) and hepatomegaly in 20 (15%) patients. Chest finding included hyperinflation (83%), kyphosis (17%), crepitations (92%), wheezing (25%) and bronchial breathing (17%).

Diagnosis

The diagnosis of CF should be suspected by the presence of a typical phenotype or family history and confirmed by the demonstration of a *high sweat chloride (> 60 mEq/L)* on repeated measurements and/or by identifying two CF causing mutations. Nasal potential difference measurements can be used as an adjunct to sweat test but is not widely available.[15]

Supportive Laboratory Tests

In the absence of sweat chloride estimation and mutation analysis at most centers in India, CF may be suspected on presence of supportive investigations. These are as follows:

1. *Abnormality in blood biochemistry and acid base status:* Patients with CF may have low or low normal serum sodium. There may be metabolic alkalosis and hypochloremia. Presence of these in a patient with typical phenotype suggests a possibility of cystic fibrosis.[14] Anemia can occur along with hypoalbuminemia and ascites as a result of vitamin E deficiency and protein malabsorption.
2. *Airway colonization:* Children with cystic fibrosis may be infected with *Pseudomonas aeruginosa, Staphylococcus aureus* or non-typable *Hemophilus influenzae.*[14] The isolation of *Pseudomonas aeruginosa* or *Burkholderia cepacia* from sputum or cough swabs with typical phenotype is suggestive of a CF diagnosis.[3] All children suspected of having CF should have specimens sent for microbiological culture to identify and treat infecting respiratory pathogens. Older children should have sputum specimens sent for culture. Young children and infants are often unable to expectorate. Culturing secretions from the airways obtained after saline inhalation and physiotherapy should therefore be attempted or else a cough swab should be sent for analysis.[15]
3. *Pancreatic function tests:* Cystic fibrosis is the commonest cause of exocrine pancreatic deficiency below 20 years of age.[16] Assessment of pancreatic function is difficult. The crude methods used are stool crematocrit estimation, digestion of X-ray films, and fecal fat estimation. More recently measurement of stool pancreatic elastase-1 has been reported as a sensitive and specific test.[17]
4. *Obstructive azoospermia:* In postpubertal boys, a semen analysis for azoospermia can be carried out. Sperm are absent in upto 98 percent of postpubertal patients with cystic fibrosis.[16]
5. *Radiological imaging:* X-ray film of the chest, sinuses and computerized axial tomography (CAT) scan of chest may show findings suggestive of CF although these are nonspecific. These investigations are more useful for monitoring diagnosed patients. X-ray film of chest may show hyperinflation, peribronchial thickening, cystic changes and lobar or segmental collapse. The

findings on CAT chest include cystic or varicose bronchiectasis, peribronchial thickening, segmental collapse, mucous impaction and subpleural bullae formation. The imaging studies of sinuses may show delayed pneumatization or mucosal thickening.

Management

The treatment of cystic fibrosis in children includes respiratory management, nutritional care, anticipation and early diagnosis of liver disease, diabetes and other organ dysfunction.

Respiratory Management

Respiratory manifestations are important cause of morbidity during childhood in children with CF. In majority respiratory illness is main cause of mortality. Lung damage in cystic fibrosis is caused by excessive poorly effective inflammatory processes in response to bacterial infection of normally sterile airways. Respiratory therapy aims to limit lung damage by decreasing the number of infecting organisms and suppressing the inflammatory process and hyperreactivity of airways. The principle components of care used to achieve this includes airway clearance techniques, antibiotics and anti- inflammatory agents.

Airway Clearance Techniques

The airway secretions are very viscid in CF. They are very difficult to clear and lead to secondary infections and damage to respiratory tract. Airways can be kept clear by adequate hydration, chest physiotherapy, judicious use of antibiotics and mucolytic agents. To keep the secretions less viscid it is important to maintain good hydration by ensuring intake of plenty of liquids and extra salt.

Chest Physiotherapy

Chest physiotherapy techniques for keeping airways clean includes following methods:

1. Postural drainage and chest clapping
2. Active cycles of breathing
3. Positive expiratory pressures (PEP)
4. High pressure PEP
5. Flutter therapy
6. Autogenic drainage
7. High frequency chest wall oscillation (HFCWO).

The method can be selected for an individual on the basis of age of patient, clinical status, experience of physiotherapist, personal preference of patients, social issues including level of support, etc. For infants and young children postural drainage and chest clapping may be more convenient.[18] Cyclical breathing and autogenic drainage requires patient's cooperation hence they can be used in older children.[19,20] Flutter therapy,[21] positive expiratory pressure and high frequency chest wall oscillation require special devices and training. They can be used under supervision of physiotherapist.

Mucolytic Agents

Various mucolytic agents have been used by oral as well as inhalation route. N- acetyl cystein breaks the sulfhydryl bonds of the mucous glycoprotein thereby reducing the viscosity of airway secretions. Because of its offensive odor and propensity to cause bronchospasm, hemorrhagic tracheitis and impaired ciliary clearance, its use is limited to selected cases where other measures fail to clear the air passage.

Recombinant Human DNAse (rhDNAse)

In CF patients, there is inordinately high concentration of DNA in respiratory secretions. This is released by disintegrating inflammatory cells. Recombinant human DNAse has been found to reduce the viscoelasticity and adhesiveness of CF sputum in animal models. Now with extensive long term trials in patients with CF, it has been proved that Dnase, given as aerosol, increases mucociliary clearance and reduces incidence of respiratory infections; it also decreases rate of hospitalization, number of days missed from work or school and the frequency of CF related symptoms. The side effects of rhDNAse are very few and mild. The side effects include upper airway irritation (voice change, laryngitis, pharyngitis), rash, chest pain and conjunctivitis. A small proportion of patients 2 to 4 percent may develop antibodies to rhDNAse. It has been recommended in doses of 2.5 mg once or twice a day.[22]

There is no role for oral mucolytic drugs such as bromhexine, ambroxole, etc.

Antibiotic Therapy (Table 30.2)

The commonly encountered microbial agents causing pulmonary exacerbation in children with CF include *Staphylococcus aureus, Hemophilus influenzae b, Pseudomonas spp, Burkholderia cepacia,* etc. Different viruses, mycoplasma, *Mycobacterium spp,* and *Aspergillus* are other important pathogens responsible for pulmonary exacerbation. It is important to select an antibiotic on basis of organisms isolated from respiratory secretions. The organisms can be isolated by obtaining cough swab, sputum or deep throat swabs after physiotherapy (DTSP). In young infants and children a deep throat swab after physiotherapy may be a good alternative specimen for isolation of organism. DTSP has been shown to correlate very well with sputum cultures in older children.[23] Periodic cough swab cultures may help in empirical treatment of acute exacerbation.

The drugs effective against common pathogens and their doses are given in Tables 30.2 and 30.3. The duration of intravenous therapy is 2 to 4 weeks. An early identification of respiratory infection and administration of oral antibiotics may decrease the need for hospitalization and intravenous antibiotics. The early indications of starting oral antibacterials include increase cough and expectoration, change in the color of expectoration, decrease in activity, impaired appetite, fever, and weight loss. Fever may not be a common clinical manifestation of acute exacerbation of infections. The treatment of acute exacerbation of infection if the patient is known to be colonized with *Pseudomonas* include ceftazidime, or cefoperazone or piperacillin or imipenam or meropenam in combination with an aminoglycoside.[24] If the colonization status is not known then a combination of drugs effective against *Pseudomonas* and *Staphylococcus* are used empirically. The commonly

Table 30.2: Organisms associated with exacerbation of pulmonary infection in patients with cystic fibrosis and appropriate intravenous antibiotic treatment

Prevalent bacteria	*First choice*		*Alternative choice**	
	Antibiotics	*Dose*	*Antibiotics*	*Dose*
S. aureus	Cephazoline	25-50 mg/kg every 6 hours	Vancomycin	15 mg/kg every 6 hours
H. influenzae and *S. aureus*	Ticarcillin–clavulanate plus	100 mg of ticarcillin per kg and 3.3 mg of clavulanate/kg every 6 hours		
	Gentamicin	3 mg/kg every 8 hours		
S. aureus and *P. aeruginosa*	Ticarcillin–clavulanate plus tobramycin Gentamicin	100 mg of ticarcillin per kg and 3.3 mg of clavulanate/kg every 6 hours 3 mg every 8 hours		
P. aeruginosa only	Ticarcillin plus Tobramycin	100 mg/kg every 6 hours 15 mg/kg every 12 hours	Tobramycin plus ceftazidime, Piperacillin or imipenem Aztreonam plus amikacin	3 mg/kg every 8 hours 50 mg/kg every 8 hours 100 mg/kg every 6 hours 15-25 mg/kg every 8 hours 50 mg/kg every 8 hours 5-7.5 mg/kg every 8 hours
P. aeruginosa and *Burkholderia cepacia*	Ceftazidime plus Ciprofloxacin	50-75 mg/kg every 8 hours 15 mg/kg every 12 hours	Ceftazidime, plus Chloramphenicol or Trimethoprim-sulfamethoxazole	50-75 mg/kg every 8 hours 15-20 mg/kg every 8 hours 5 mg of Trimethoprim/kg IV and 25 mg of sulfamethoxazole/kg every 6 hours
B. cepacia only	Chloramphenicol or Trimethoprim-sulfamethoxazole or both	15-20 mg/kg every 6 hours 5 mg of trimethoprim/kg and 25 mg of sulfamethoxazole/kg every 6 hours		

Table 30.3: Oral antibiotics commonly used to suppress respiratory pathogens in patients with cystic fibrosis

Pathogen	Antibiotics	Doses
S. aureus	Cloxacillin	12.5 mg/kg every 6 hours
	Cephalexin	12.5 mg/kg every 6 hours
	Amoxicillin clavulanate	10-15 mg of amoxicillin/kg and 2.5-3.75 mg of clavulanate/kg every 8 hours
	Erythromycin	15 mg/kg every 8 hours
	Clarithromycin	7.5 mg/kg every 12 hours
H. influenzae	Cefaclor	10-15 mg/kg every 8 hours
	Amoxycillin	10-20 mg/kg every 8 hours
S. aureus and *H. influenzae*	Cefixime	10 mg/kg/day
	Amoxicillin-clavulanate	10-15 mg of amoxicillin/kg and 2.5-3.75 mg of clavulanate/kg every 8 hours
	Trimethoprim–Sulfamethoxazole	5 mg of trimethoprim/kg and 25 mg of sulfamethoxazole/kg every 12 hours
	Cefpodoxime	5 mg/kg every 12 hours
	Cefuroxime	20 mg/kg every 12 hours
P. aeruginosa	Ciprofloxacin	20-30 mg/kg/day in 2-3 divided doses
	Ofloxacin	Not approved
B. cepacia	Trimethoprim-sulfamethoxazole	5 mg of trimethoprim/kg and 25 mg of sulfamethoxazole/kg every 12 hours

used oral antibiotics include a drug from fluroquinolones. These drugs may be started early and given for 2 to 3 weeks when acute exacerbation is suspected.

Aerosolized Antibiotics

The airways of CF patients get colonized with *Pseudomonas spp.* and may be responsible for frequent exacerbation. Complete eradication of *Pseudomonas* from airways of CF patient is extremely difficult. Now, with the availability of effective antipseudomonas drugs; frequent exacerbations of chest infections in these patients can be decreased by reducing the colonization. Recently use of aerosolised antibacterials has been shown to give good results in treating patients who are chronically colonized with pseudomonas.[25-27] The drugs commonly used are gentamicin and tobramicin in doses of 40 to 80 mg by aerosol two to three times a day (Table 30.4). Higher doses upto 600 mg thrice a day have also been used. The drugs are delivered to lower respiratory tract by nebulizers. The drugs are continued for 3 to 6 months or till the two consecutive cough swabs or sputum cultures are negative for *Pseudomonas*. In a recent study on 520 patients (mean age 21 years) of cystic fibrosis the patients were treated with 300 mg of tobramycin or placebo twice daily followed by 4 weeks with no study drug it was concluded that intermittent administration of tobramycin was well tolerated and improved pulmonary function, decreased the density of *P. aeruginosa* in sputum and decreased the risk of hospitalization.[27]

Table 30.4: Dosage of inhaled antibiotics given by nebulizer

Drug	Age (years)	Dose (mg)	Frequency (per day)
Tobramycin	< 2	40	2
	> 2	80	2
	> 12	160	2
Gentamicin	< 2	40	2
	> 2	80	2
	> 12	160	2
Colistin sulfomethate	< 6	0.5*	2
	> 6	1.5*	2
	< 12	500	2
	> 12	250	2
Amphotericin		10	2–4

Mega units

Bronchodilator and Inhalation Steroid Therapy

Bronchial hyperresponsiveness occurs in 25 to 50 percent patient particularly during intercurrent infections and in those with poor baseline lung function. Some patient may have atopic asthma as well as cystic fibrosis. Factors that are associated with atopic asthma include: exercise induced wheezing, persistent nocturnal coughing, cough or wheeze following exposure to allergens, concomitant eczema and/or rhinitis and family history of asthma. These patients may benefit with bronchodilators and inhaled steroids. These patients should be treated for asthma on usual guidelines.[28]

In case a child develops respiratory failure, mechanical ventilation will be required. The ventilator settings would need to be individualized depending on the major underlying lung pathology. Most of these children will have obstructive component and some may have consolidation due to infection. Minimum tidal volumes should be used. PEEP should be optimized and a long expiratory period should be used to avoid hyperinflation.

Nutritional Management of CF

The main aim of nutrition management is to achieve normal growth and development of children. Nutritional management of CF can be discussed as follows:

i. Increasing caloric intake
ii. Supplement fat soluble vitamins
iii. Replace pancreatic enzymes.

Increase Caloric Intake

Most children will grow normally by consuming the average energy intake requirement for a child of their age group provided that they get adequate enzyme supplements. The caloric need increases in situations with persistent chest infection or frequent pulmonary exacerbations. Caloric demand may increase upto 50 percent during acute pulmonary exacerbation.[29] In Indian children where diagnosis of CF is delayed, malnutrition is common and by the time diagnosis of CF is made, their airways are colonized with *Pseudomonas* and they suffer from frequent exacerbations. Enzyme supplements are inadequate. Hence they need more calories than their normal peers. Caloric intake can be increased by encouraging the child to eat energy rich food throughout day, e.g. full fat dairy products and fried food. Parents should be told not to restrict fat in the child's diet.

Oral caloric supplements In addition to caloric needs supplementary feeds by using commercial preparations or homemade feeds can be used. The recommended oral caloric supplement for different age groups is given in Table 30.5.[29]

Table 30.5: Recommended caloric supplements

Age	Per day caloric supplement
1-2 years	200 k cal
3-5 years	400 k cal
6-11 years	600 k cal
More than 12 years	800 k cal

It should be kept in mind that the caloric supplements are given in addition to the regular meals. For Indian children caloric supplements can be given by using locally available food. Suggested supplements include – addition of skimmed milk powder and ice cream to milk, preparations of groundnut and jiggery, coconut and sugar etc.

Nasogastric and gastrostomy feeding In some patients short-term/long-term nasogastric or gastrostomy feeding is required. Indications for nasogastric feeding are as under:

1. No weight gain for 6 months even with adequate caloric intake,
2. Acute pulmonary exacerbation with poor oral intake,
3. Consistently poor appetite and inability to maintain caloric intake,
4. Before major surgical procedures,
5. During periods of increased caloric requirement e.g. puberty and pregnancy.

The feeds may be homemade liquid feeds or commercially available formulae. Pancreatic enzymes should always be given with supplementary feeds.[30]

Supplementation of Fat-soluble Vitamins and Minerals

Children with pancreatic insufficiency are at risk of developing deficiency of fat-soluble vitamins. Survey of older children with CF receiving standard pancreatic enzyme replacement and multivitamins have reported biochemical deficiency of vitamin A in 20 to 46 percent, vitamin D in 25 to 30 percent, vitamin E in 95 percent and vitamin K in 50 percent of patients. Deficiency of one or more vitamins may be present in 40 percent children between the age of 4 to 8 weeks. Even after enzyme replacement; deficiency of fat-soluble vitamins may be present in some children.[31]

Recommended doses of vitamin A and D are given in Table 30.6. Recommended doses of vitamin E are 50 mg for children below one-year of age, 100 mg for children between 1 to 10 years and 200 mgs thereafter. Vitamin K is not recommended routinely. In children with clinical manifestation of vitamin K deficiency and those having liver disease a dose of 10 mg vitamin K daily is recommended. All vitamins should be given with meals and enzyme. Water-soluble vitamin deficiency is not common. Regular dietary assessment should prevent this situation occurring.[29]

Table 30.6: Recommended doses of Vitamin A and D

[illegible]	[illegible]	[illegible]
Less than 6 weeks	2000 IU	200 IU
6 weeks to 6 months	4000 IU	400 IU
More than 6 months	8000 IU	800 IU

Use of iron, zinc, and selenium supplements has been of interest, although their value remains uncertain. Average daily intake should achieve reference value.

Salt loss in sweat is excessive in CF patients. Increased sweating in hot weather may result in clinical manifestations of hyponatremia.[32] Sodium supplement is recommended in hot climate. There are no studies on the doses of daily salt for Indian children. Till data are available we advice daily extra salt intake of 2.5g in children below 10 kg, 5 g in children between 11 to 20 kg and 7.5 g in children above 20 kg.

Pancreatic Enzyme Supplementation

Regular enzyme supplement in form of enteric-coated spherules has improved nutritional management significantly. The enzyme preparation is given with meals. The pancreatic supplements can be given in form of capsules or the spherules can be sprinkled over food in infants and young children who are not able to swallow capsules. The initial doses of enzyme can be 3000 (one-third capsule)–10000 IU (one capsule) per meal. Doses can be adjusted by observing stool consistency and weight gain in the child.[32] Appropriate pancreatic replacement therapy will achieve normal or near normal absorption. It is important to identify both malabsorption and evidence of a pancreatic insufficiency in all patients who are to receive pancreatic enzymes. All who have evidence of fat malabsorption are deemed pancreatic insufficient and candidates for enzyme replacement therapy. Effective treatment should allow a normal diet to be taken, control symptoms, correct malabsorption and achieve a normal nutritional state and growth.

The occurrence of fibrosing colonopathy in some patients receiving very high doses of those enzymes that have the copolymer (Eudragit L30 D55) in their covering has resulted in guidelines in the UK to avoid dosages greater than the equivalent of 10,000 IU lipase/kg/day for all patients and also to avoid preparations containing this copolymer in children and adolescents. For patients not responding to 10,000 IU lipase/kg/day, review of adherence to treatment, change of enzyme preparation, variation of the time of administration and reduction in gastric acid may improve absorption. The importance of excluding other gastrointestinal disorders as a cause of the patient's symptoms and the need for early investigations, rather than merely increasing the dosage of enzymes, is stressed. With modern enzymes, adequate control of gastrointestinal symptoms and absorption can be achieved at dosages of 10,000 IU lipase/kg/day or only slightly more, and a normal nutritional state and growth rate maintained in most patients with cystic fibrosis.[33]

There has been a search for a cheaper source of lipase as the current enzyme preparations are quite expensive. Tursi *et al.* have demonstrated significant lipolytic activity in dehulled oats.[34]

Management of other Gastrointestinal (GI) Manifestations of CF

The common GI manifestations in CF include pain abdomen, abdominal distention, meconium ileus equivalent, intussusception, meconium peritonitis.

Pain abdomen in CF may be due to pancreatic insufficiency, rectal prolapse, gastroesophageal reflux, or intestinal obstruction. Pain and abdominal distention, rectal prolapse due to pancreatic insufficiency respond after increasing doses of enzymes.

For gastroesophageal reflux prokinetic agents along with H-2 receptor antagonist are required. Pain abdomen secondary to constipation can be treated with oral lactulose in doses of 1 ml/kg/day in 2 divided doses.

Management of meconium ileus during neonatal period and meconium ileus equivalent includes maintenance of fluid and electrolyte balance, administration of hyperosmolar solutions (Gastrograffin) perorally or by enema and bowel washes in some patients. Meconium peritonitis and unresponsive meconium ileus may need surgical intervention.[35]

Management of Liver Disease in CF

With improved survival, liver involvement in CF is recognized more frequently. Early administration of ursodeoxycholic acid (UDCA) may improve outcome of liver disease in children with CF. Ursodeoxycholic acid is effective in improving cholestasis and hepatic dysfunction in nodular biliary cirrhosis and, also, in reversing the early sonography findings suggestive of focal biliary cirrhosis.[36] It is speculated that ursodeoxycholic acid may prove to affect the natural history of cystic fibrosis-related liver disease.[36] A regular monitoring of liver function test and imaging studies should be part of management.

Assessment and Monitoring

The assessment of illness and monitoring for progress of illness can be done by clinical examination and various laboratory tests. The assessment may be annual or continuous.[37]

Clinical Assessment

Various clinical scoring systems have been developed to provide both a numerical assessment of patient's status and a way of documenting progress in response to treatment. The Shwachman-Kulezyeki score is the most widely used one.[38] In this scoring system, 25 points are given for each of the following categories; activity level, nutritional status, physical examination and chest radiograph changes. Points are deducted for deterioration in status; 100 is optimal and the lower the number; worse is the clinical condition.

Laboratory Assessment

These include periodic pulmonary function test, X-ray film of chest, chest CT scan, ultrasound abdomen, echocardiography, blood chemistry such as glucose, calcium, vitamin levels, transaminases levels, etc. Frequency of these test depend on the severity of illness and age of patients.

Emerging Therapies

Antiprotease Therapy

Pulmonary inflammation in CF is caused by recurrent and persistent Gram-negative infections. Due to this, there is accumulation of neutrophils in the airways. On lysis, they release their lysosomal granules that contain hydrolytic enzyme such as elastase which is a potent proteolytic agent. Excessive elastase burden in lungs is the probable cause of airway destruction and bronchiectasis. The use of aerosolized alpha 1 antitrypsin, with an aim to neutralize the effects of elastase, has shown encouraging results.[39] In future, the use of recombinant secretory leukoprotease inhibitor SLPI may be used to decrease the lung destruction in patients of CF.[40]

Gene Therapy

CF is caused by mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Consequent to mutations in parental genes; airway epithelial cells have insufficient CFTR function. Because this can be corrected *in vitro* by transfer of the normal CFTR gene into airway epithelial cells, it is reasonable to hypothesize that the respiratory manifestations of CF could be prevented by transfer of the normal CFTR cDNA to airway epithelium *in vivo*. Over last few years Krost *et al*[41] have developed a strategy to accomplish this goal using a replication deficient El E3 recombinant adenovirus (Ad) serotype 5 vector containing the normal human CFTR cDNA (AdCFTR). Studies with experimental animals demonstrated that with administration of such a vector in the airways, the human CFTR cDNA could be transferred to the airways epithelium, with expression of the human CFTR cDNA for at least 6 weeks. Extensive preclinical studies *in vitro* and *in vivo* demonstrated that the risk to humans were sufficiently low. There are evidence that it is feasible to transfer and express the normal CFTR cDNA to the airway epithelium *in vivo* in individuals with CF.

A phase I clinical trial was conducted in which recombinant adenovirus containing the cystic fibrosis transmembrane regulator (CFTR) (Ad2/CFTR) was administered by bronchoscopic instillation or aerosolization to the lungs of cystic fibrosis (CF) patients.[42] In this study, the efficiency of Ad2/CFTR-mediated transduction of bronchial airway cells was evaluated. The authors concluded that aerosol administration is a feasible mean to distribute adenoviral vectors throughout the conducting airways, but improvements in adenovirus-mediated transduction of airway epithelial cells are necessary before gene therapy for CF will be effective. Also, in some cases, a high percentage of nonepithelial mononuclear cells or squamous metaplastic epithelial cells was infected with the adenoviral vector.[42]

Role of Aminoglycosides in Promoting Expression of CFTR

Premature stop mutations account for approximately 5 percent of all mutant alleles in CF patients. The aminoglycoside antibiotics can increase the frequency of erroneous insertion of the nonsense codon, thereby permitting protein translation to continue to the normal end of the gene. Wilschanski *et al* have demonstrated significant depolarization of the nasal epithelium after nasal gentamicin instillation for 2 weeks in 9 CF patients carrying stop mutations.[43] This represents improvement in Cl^- transport due to expression of CFTR. Inhaled gentamicin may lead to expression of CFTR in lung epithelia; this still needs to be studied.

Heart Lung Transplantation

For patients with very advanced lung disease and poor life expectancy, lung transplantation has been used. Initially this form of treatment was developed using heart lung transplantation.[44] More recently, single lung transplant have been developed.[44] These have prolonged the life of the patients and the 2-year survival rate is 50 to 60 percent.[45]

Aerosol Amiloride Therapy

The characteristic abnormality of CF airways function is the increased absorption of sodium and water across the epithelial barrier. Sodium enters the cells through apical channels that can be blocked by amiloride. Aerosolized amiloride in adult patients showed an improvement in the viscosity and elasticity of sputum during the treatment period.[46] More recently amiloride has been evaluated in a multicenter randomized double-blind placebo-controlled trial.[47] 137 patients of cystic fibrosis aged more than 5 years (n=137) whose forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), and forced midexpiratory flow (FEF_{25-75}) were not below 50 percent, 50 percent and 30 percent of reference values, respectively were studied. At the end of the 6-month treatment period, the effects of the amiloride treatment on FVC and secondarily on FEV_1, FEF_{25-75}, the number of days on antibiotic therapy, the Shwachman score, the change in sputum bacterial flora, and nocturnal cough were assessed. This study failed to demonstrate any significant benefit of amiloride over placebo on FVC, FEV_1, and the other secondary endpoints in the studied population.

Passive Immunotherapy

Passive immunotherapy with hyperimmune gammaglobulin that delivers opsonizing immunoglobulin G antibodies against *P. aerugenosa* surface soluble antigens may aid phagocytosis and reduce bacterial density in the airways. Other suggested benefits of passive immunotherapy are exoproduct netralization and decreased immune complex deposition resulting in less tissue injury.[48]

Anti-inflammatory Treatment

Anti-inflammatory medications in form of steroids and nonsteroidal anti-inflammatory drugs have shown improvement in pulmonary disease. A randomized control trial of inhaled steroids did not show improvement in cystic fibrosis.[49] Oral corticosteroids at a prednisolone equivalent dose of 1 to 2 mg/kg alternate days appear to slow the progression of lung disease in CF but this benefit needs to be weighed against the occurrence of adverse events, in particular, development of cataracts and effect on linear growth. A risk/benefit analysis of low-dose alternate days corticosteroids would be important and the role of short-term use of oral steroids should be more fully evaluated.[50]

There is preliminary evidence to suggest that non-steroidal anti-inflammatory drugs may prevent pulmonary deterioration in subjects with mild lung disease due to cystic fibrosis, currently their routine use cannot be recommended. Further trials are required to confirm that their use prevents pulmonary deterioration and is associated with improved nutritional status. Such trials should also address the age group of subjects most likely to benefit, the prevalence of important adverse effects and the optimal dosage schedule as well as any reduction in concomitant therapy.[51]

A recent randomized double blind crossover placebo controlled trial in 41 children with cystic fibrosis showed a statistically significant improvement in FEV_1 in the children receiving azithromycin.[52] The treatment group had a lower need for oral antibiotic courses. The potential mechanism may be anti-inflammatory, antibacterial, decrease in biofilm synthesis, etc.

Prenatal Diagnosis

With the identification of genetic mutations in a child and parents, now it is possible to make a prenatal diagnosis by chorionic villous (CV) biopsy around 10 to 12 weeks or amniotic fluid cell culture at 15 to 16 weeks of gestation in future pregnancies, in addition pre-implantation diagnosis is also possible.[53-55] However, because the current median life expectancy for patients with CF in best centers exceeds 30 years, many parents may not opt for therapeutic abortions in presence of affected fetus. Hence prenatal diagnosis of CF is going to remain medical dilemma for many years to come.

Prognosis

The median life expectancy for cystic fibrosis is now over 30 years, and it is projected that in newborn infants it will become more than 40 years. With the identification of the cystic fibrosis gene and its product, cystic fibrosis transmembrane conductance regulator (CFTR), it has been possible to discover the wide-spectrum of the disease from the classical case of the infant with cystic fibrosis to the elderly childless man with unexplained bronchiectasis. There is increasing evidence of the advantages of newborn screening for cystic fibrosis and subsequent specialist care. Management concentrates on optimizing nutritional status and preventing lung infection and inflammation.[56] Results of a study on prediction of survival of children with cystic fibrosis and severe lung disease suggests that a 12 year old male child with an FEV_1 of 30 percent predicted and a SaO_2 of 85 percent has a 44 percent risk of death within 2 years [95% confidence interval (CI) 35-54%], whilst a female child with the same measurements has a 63 percent risk of death [95% CI 52-73%] within the same period.[57] Survival analysis of Indian children with CF suggest that early mortality was associated with early onset (below 2 months) of symptoms, severe malnutrition at the time of diagnosis, more than four episodes of pulmonary exacerbations in a year and colonization with *Pseudomonas*.[8]

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CHAPTER

31

Neonatal Congenital Lung Lesions

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Congenital malformation of lungs are rare. Most congenital lung problems are commonly diagnosed in the newborrn period, however, not all of them present with clinically significant problems at birth. Following is a discussion related to common congenital malformations of lungs:

1. Congenital diaphragmatic hernia (CDH)
2. Pulmonary sequestration
3. Congenital lobar emphysema
4. Bronchogenic cysts
5. Congenital cysticadenomatoid malformation (CCAM)
6. Tracheoesophageal fistula.

CONGENITAL DIAPHRAGMATIC HERNIA (CDH)

Incidence of Congenital diaphragmatic hernia (CDH) is reported to be one in 2000 to 5000 births. The expected recurrence risk in a first degree relative is approximately 2 percent.[1] Approximately one-third of infants with CDH have associated fetal congenital anomalies and are still born.[2] Associated anomalies are present in approximately 30 percent of live born cases. Neural tube defects, cardiac defects are the most common associations. 80 percent lesions are present on left side and 20 percent on right side. Bilateral lesions are rare. 10-15 percent of CDH have hernial sac formed from parietal pleura and peritoneum. CDH is associated with pulmonary hypoplasia which is more severe on the ipsilateral side[3] and pulmonary hypertension. Acidosis, hypothermia and stress further aggravate pulmonary hypertension. The degree of pulmonary hypoplasia determine the clinical presentation and ultimate long term outcome of the process.

Diagnosis and Management

CDH is often diagnosed on a prenatal ultrasound examination. Polyhydramnios is present in 80 percent cases of CDH. After birth large majority demonstrate respiratory symptoms within the first 24 hours of life. On examination these children have asymmetrical funnel chest with scaphoid abdomen and decreased respiratory movements on side of hernia, respiratory distress, displaced apex beat. Mediastinal shift may also obstruct venous return resulting in hypotension and inadequate peripheral perfusion.

A plain chest radiograph is often diagnostic (Fig. 31.1). It shows intestinal loops in chest, absence of gastric bubble in abdomen, shift of mediastinum to opposite side. Position of stomach can be confirmed by placing a nasogastric tube. Upper gastrointestinal contrast study may rarely be required.

Once diagnosis is confirmed, *echocardiography, abdominal* and *cranial ultrasound* should be done to rule out associated anomalies. 5-25 percent of CDH present late; from 1 month–adulthood, with recurrent mild respiratory illness, chronic pulmonary disease, pneumonias, effusion, empyema or gastric volvulus. The differential diagnosis includes eventration of diaphragm, anterior diaphragmatic hernia of Morgagni, congenital esophageal hiatus hernia, congenital cystic disease of lung, primary agenesis of lung.

Prognostic Factors

Prognosis in these children depends on various anatomical and physiological factors and pulmonary

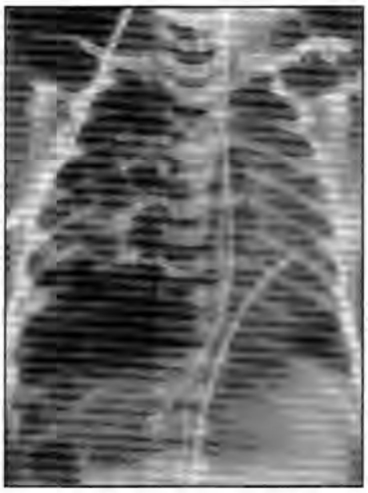

Fig. 31.1: Chest radiograph showing diaphragmatic hernia

function parameters. Prognosis is less favourable if antenatal diagnosis is made at < 24 weeks of age, associated anomalies are present, defect is large or is right sided, left ventricular hypoplasia is present. The baseline levels of the various preductal and postductal ABG parameters and their improvement or lack of improvement with ventilation, alveolar–arterial O_2 gradient, and the various ventilatory indices have been used to predict the outcome.[4] Preoperative measurement of functional residual capacity may predict fatal pulmonary hypoplasia. Pre and post operative pulmonary functional tests help in identifying infants that might require ECMO therapy.

Delivery

In cases where the lesion is diagnosed antenatally the delivery should be conducted at a tertiary care center where the neonatologists with full array of respiratory care strategies (including high frequency ventilation and nitric oxide) are available. A spontaneous vaginal delivery is preferred.

CDH is physiological emergency and not a surgical emergency. Respiratory distress in these cases results from the uncorrectable pulmonary hypoplasia and potentially reversible pulmonary hypertension.

Management at Birth

The therapeutic interventions are directed at preventing or reducing pulmonary hypertension.

After birth endotracheal intubation is performed and nasogastric tube is inserted. Ambu bagging is contraindicated to avoid distension of thoracic stomach and intestine. Arterial and venous lines are placed in for central venous pressure monitoring, pre and post ductal arterial blood gases. If the infant is unable to saturate the preductal blood fully with oxygen and maintain PCO_2 to less than 50 torr, it generally indicates severe pulmonary hypoplasia incompatible with life. During resuscitation efforts should be directed towards avoiding episodes of hypoxia and systemic hypotension and correction of acid-base imbalance. Ventilatory support should be aimed at achieving a preductal PO_2 of greater than 60 torr and PCO_2 of less than 60 torr. Extremes of hyperventilation with induced alkalosis should be avoided. If conventional mechanical ventilatory techniques cannot reverse the hypoxemia or hypercarbia, high-frequency techniques using either jet ventilator or oscillating ventilator may be required.[5,6]

Of the various pharmacological agents tried to manage pulmonary hypertension, tolazoline has been found to be marginally effective whereas drugs such as nitroprusside, isoproteranol, nitroglycerine, captopril and prostaglandin have not been effective.[7-9] Reports on efficacy of nitric oxide, which has been useful in cases of persistent pulmonary hypertension of new born, are mixed.[10,11]

Newer pulmonary vasodilators such as sildenafil show promising results however large randomized trials are lacking. Patient should be taken up for surgery only after preoperative stabilization.[12,13]

Operative Repair

Surgical repair can be done through abdominal, thoracic or combined approach. Prosthetic material may be needed to cover a large diaphragmatic defect. If abdomen is unable to accommodate the erstwhile-herniated gut, a ventral hernia may be created to achieve simple skin closure. The ventral hernia can be repaired at a later date. Post operatively the care remains same as before operation. Severe pulmonary hypertension is common in the postoperative period, requiring various ventilation strategies in the NICU to control hypercabia and avoid hypoxemia.

Results

Overall survival of neonates with CDH remains 50-80 percent even with use of modern ventilatory strategies and ECMO.[14,15] On post operative follow up chest radiographs may show persistent hyperlucency because of increased alveolar distension and decreased vascularity. They may have mild restrictive airway disease that may improve with time.[16] Mental retardation and neurological deficit may result from cerebral hypoxia. The survivors have a high incidence of gastroesophageal reflux and foregut dismotility,[17,18] skeletal defects such as pectus anomalies and scoliosis.[17]

Future Therapies

The newer modalities of management that are being worked on are fetal surgery, PLUG therapy, liquid ventilation techniques, lung transplantation and antenatal hormone therapy.

Eventration of Diaphragm

It can be congenital or acquired due to paralysis of phrenic nerve. They present in a manner similar to CDH though the symptoms are less severe. The diaphragmatic muscle is present but is attenuated and inactive giving rise to paradoxical movements on respiration. Diagnosis is made on fluoroscopy of chest. CT or MRI may be done. A small eventration can be left untreated but a large eventration should be repaired promptly even if asymptomatic.

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PULMONARY SEQUESTRATION

Introduction

It is defined as a segment of non-functioning lung tissue that has no identifiable bronchial communication and receives its blood supply from anomalous systemic arteries. The blood supply is anomalous, single or multiple vessels may be encountered.[1] The 2 forms of pulmonary sequestration include intrapulmonary, which is surrounded by normal lung tissue, and extra pulmonary, which has its own pleural investment. Other congenital malformations may also be present. It accounts for approximately 6 percent of all congenital pulmonary malformations.[2]

Extrapulmonary Sequestration

Extrapulmonary sequestrations are masses composed of non-functioning primitive pulmonary parenchymal tissue that have no connection to the tracheobronchial tree. The mass lies outside of the normal investment of visceral pleura and is seen in a subdiaphragmatic position in 10 percent of cases[3]. They consist of uniformly dilated bronchioles, alveolar ducts and alveoli, which form the bulk of the lesion, although bronchial structures may be absent. Extra pulmonary sequestrations occur on the left in 95 percent of cases with a male: female ratio of 4: 1. Of these, 75 percent are found between the left hemi diaphragm and the left lower lobe. 8 percent of lesions are subdiaphragmatic and can mimic masses arising in various organs, such as the adrenal gland.

The arterial supply is predominantly via systemic arteries (95%) rather than pulmonary arteries (5%); the systemic arteries are commonly branches of the thoracic aorta or the abdominal aorta (80%). In rare cases, the supply may be from anomalous vessels arising from the splenic, gastric, subclavian, and intercostal vessels. Venous drainage also occurs most commonly via the systemic veins (75%), for example, the inferior vena cava (IVC) or azygos or portal veins rather than pulmonary veins (25%).

Extrapulmonary sequestration is widely accepted to be congenital in origin. An accessory lung bud develops from the ventral aspect of the primitive foregut. The accessory lung bud migrates caudally with the foregut and receives its blood supply from the splanchnic plexus, as does the foregut. If the bud arises after the pleurae have developed, it is not incorporated within the lung visceral pleura, and an extrapulmonary sequestration is formed.

Most of the cases of extrapulmonary sequestrations present in infancy and are associated with other congenital abnormalities in as many as 65 percent of patients. The most common association is with diaphragmatic hernias (20%); others include congenital cystic adenomatoid malformation (CCAM), bronchogenic cysts, and foregut malformations.

Intrapulmonary Sequestration

Intrapulmonary sequestration is also a nonfunctioning area of pulmonary parenchyma and usually is not in communication with the tracheobronchial tree; however, it may contain air via the pores of Kohn or a connection to normal small bronchi. It is incorporated within the normal visceral pleura of the lung. Intrapulmonary sequestrations usually contain dense fibrous parenchyma, which has replaced the normal pulmonary tissue as the result of chronic inflammation and fibrosis. Multiple fluid containing cysts are present; the pleura is thickened by adhesions to mediastinal and diaphragmatic parietal pleura.

Intrapulmonary sequestrations form more than 90 percent of sequestrations, and 60 percent of these are found in the posterior basal segment of the left lower lobe. Overall, 98 percent occur in the lower lobes.[4] Bilateral involvement is uncommon. It is not commonly associated with other congenital anomalies.

The arterial supply is systemic in origin and is via the descending thoracic aorta (73%), the abdominal aorta or celiac axis artery (21%), and the intercostal arteries (4%). Venous drainage occurs via the pulmonary veins in majority; in 5 percent of patients, venous drainage occurs via the IVC, the superior vena cava (SVC), the azygos systems, or the intercostal veins.

The origin of intrapulmonary sequestration has been described in the past as congenital and is explained by the accessory lung bud theory. The accessory lung bud was believed to arise prior to development of lung visceral pleura, and thus, it was included within the pleura. The lack of association with other congenital anomalies, coupled with the later age at presentation and the associated infective and fibrotic changes revealed on histologic analysis, has led to the theory that intrapulmonary sequestration may primarily be an acquired post inflammatory process. The current widely held theory is that ILS is acquired after one or more episodes of necrotizing pneumonia result in obliterative bronchitis and obstruction of a lower lobe bronchus. This phase is followed by interruption of the pulmonary arterial supply to the infected lung parenchyma and hypertrophy of the systemic arterial supply from the thoracic aorta within the inferior pulmonary ligaments. The diaphragmatic pleural supply involves the celiac axis aorta and abdominal aorta, and these vessels also may be recruited. Venous drainage remains via the pulmonary veins.

Clinical Details

Extrapulmonary Sequestration

Although children with ELS can present at any age, 60 percent present in the first 6 months of life. Many lesions are diagnosed coincidentally during imaging investigations for surgery of associated congenital anomalies. Some pulmonary sequestrations are detected in utero; maternal polyhydramnios, fetal ascites, and hydrothorax may indicate the diagnosis.[5] Some patients may present with feeding difficulties related to a communication between the ELS and the GI tract. In addition, patients with ELS may present with recurrent chest infections, similar to patients with ILS. Symptoms can occur as a result of other associated anomalies, which are present in 40-60 percent of patients.

Intrapulmonary Sequestration

ILS appears in older patients, with more than 50 percent occurring after adolescence[6]. Symptoms in neonates and infants are rare, and 15 percent of ILSs are asymptomatic at diagnosis. The commonest presentation is persistent cough and recurrent chest infections. Symptoms may occur from associated anomalies in approximately 11 percent of patients. Anomalies of the chest wall may be acquired as a result of chronic lung infection. Physical examination may reveal signs of pulmonary consolidation. Rarely, auscultation may identify a bruit or continuous murmur over the sequestered lung segment from a large systemic blood supply. Patients with ILS can rarely present with massive spontaneous hemorrhage, which is potentially fatal.

Diagnosis

The diagnosis of pulmonary sequestration is made based on the clinical picture in association with the radiological evidence.

Chest X-ray

Chest radiographs can provide a reasonable diagnostic clue to pulmonary sequestration. A mass in the posterobasal segment of the left lower lobe of the lung in young patients with recurrent localized pulmonary infections is suggestive of ILS.[7] When such a lesion resolves incompletely with appropriate medical treatment, an underlying sequestration should be considered. With secondary infection it may appear as a uniform consolidation with parapneumonic effusion. It is difficult to distinguish intrapulmonary from an extrapulmonary lesion on the chest X-ray.

CT Scan

The CT scan can provide a diagnosis in 90 percen of cases.[8] The role of CT is to define vascula anatomy and to provide supporting evidence tha opacities depicted on chest radiographs or antenata sonograms may be sequestrations. Powerfu computing with 3-dimensional (3D) reconstruction provides excellent spatial resolution and definition of the spatial relationships of structures, which can obviate invasive angiographic procedures.

MRI and MR Angiography also serve the same purpose with better definition of the arterial supply and the venous drainage.[9] Barium study is indicated in patients with coexistent gastrointestinal symptoms because communication between a sequestration and the GI tract can occur.

Ultrasound

Ultrasonography is useful in prenatal diagnosis of pulmonary sequestration and its complications, in assessing progression, and in forming a prognosis, which in turn is important for appropriate parental counseling and fetal therapy. Serial prenatal sonograms are necessary in patients in whom pulmonary sequestration is suspected to search for poor prognostic factors such as increasing mediastinal shift and increasing size of the sequestration.[10] In fetuses with chest masses, 8 percent have additional structural abnormalities and an abnormal karyotype. In ELS, 65 percent of patients have associated anomalies, such as an accessory spleen, congenital heart disease, or a diaphragmatic hernia. In patients with ELS, complications can include tension hydrothorax, polyhydramnios, and hydrops fetalis.[11]

Management

Surgical resection is the treatment of choice for patients who present with infection or symptoms resulting from compression of normal lung tissue. Extrapulmonary lesions usually can be excised without loss of normal lung tissue. Intrapulmonary lesions often require lobectomy because the margins of the sequestration may not be defined clearly. Management of an asymptomatic pulmonary sequestration with no connection to the surrounding lung is controversial; however, most people advocate resection of these lesions because of the likelihood of recurrent lung infection, the need for larger resection if the sequestration becomes chronically infected, and the possibility of hemorrhage from arteriovenous anastomoses. In the absence of perioperative complications, surgical resection of the abnormal segment usually is curative.

Transarterial embolization of the aberrant arterial supply to an ILS has also been used as a definitive procedure or as a preoperative procedure to minimize the risk of vascular complications during resection.[12]

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CONGENITAL LOBAR EMPHYSEMA

Introduction

Congenital lobar emphysema (CLE) is an unusual disorder of lung characterized by overexpansion of a pulmonary lobe with resultant compression of the remaining ipsilateral lung.[1] Mediastinal shift away from the increased volume lung can also compress the contralateral lung. The term emphysema is a misnomer as there is no emphysematous destruction of alveoli; in fact in some variants there may be a striking increase in the number of alveoli (polyalveolar).[2] Thus it has been suggested that the term congenital lobar hyperlucent lobe be used. CLE is more common in males and almost always involves one lobe: left upper lobe in 41 percent, right middle lobe in 34 percent and right upper lobe in 21 percent. Upto 20 percent have bilateral involvement CLE has 2 forms.

1 Hypoalveolar (fewer than expected number of alveoli)
2 Polyalveolar (greater than expected number of alveoli)

Approximately 10 percent of patients have associated anomalies; congenital heart disease is primary among them. Pulmonary arteries are normal in patients with CLE.

Pathophysiology

Over distension of the airspaces within a pulmonary lobe is associated with air trapping and compressive changes in the remainder of the lung Mediastinal shift away from the increased volume results in compression of the contralateral lung. The abnormality is congenital related to a bronchial narrowing that is intrinsic.[3] In these cases there is weakened or absent bronchial cartilage, so that there is inspiratory air entry but collapse of the narrow bronchial lumen during expiration. This bronchial defect results in lobar air trapping. In the case of congenital extrinsic compression, such as by a large pulmonary artery, affected cartilage rings are malformed, soft, and collapsible in response to the long term in utero extrinsic effect.[4,5] CLE has an unexplained cause in some patients. Other possible causes are either an intrinsic parenchymal elastin defect or fibrosis of the interstitium such that normal expiration and reduction of lobar volume cannot occur.[6]

Clinical Features

It generally presents at birth with subtle or obvious respiratory distress in an otherwise normal infant.[7] There may be asymmetry of chest and abdominal retractions on inspiration. Hypoxemia may occur in severely affected patients. The diagnosis is often suspected upon in utero sonography if an over expanded lobe filled with fluid is identified.[8] Progressive respiratory distress from birth reflects the degree of emphysema; symptoms are at their worst in the first month. Occasionally, patients present in later childhood or adulthood with respiratory distress and repeated chest infections. Less severely affected patients may be coincidentally picked up on chest X-ray in infancy and childhood.

CLE must be differentiated from following conditions:

Bronchial mucous plug with associated hyperaeration
Extrinsic bronchial compression
Agenesis/hypogenesis of contralateral lung
Bronchial hypoplasia with air trapping peripherally
Congenital cystic adenomatoid malformation
Pneumothorax

Similar Congenital Lung Conditions

Intrinsic Bronchial Obstruction

i. Bronchomalacia may be acquired in small infants undergoing ventilation for long periods.
ii. Redundant bronchial mucosa
iii. Mucus plug
iv. Torsion of bronchus
v. Bronchial atresia

Extrinsic Bronchial Obstruction

i. Enlarged heart chamber
ii. Aneurysmal dilatation of major vessels
iii. Bronchogenic cysts and lymphadenopathy

Alveolar Fibrosis

- Congenital
- Secondary to pulmonary infection

Focal Pulmonary Hypoplasia

Resulting from diminished number of bronchioles which leads to over distension of alveoli. There is hyperlucency on chest X-ray but minimal mediastinal shift or compression of adjacent lung.

Polyalveolar Lobe

The number of bronchial bronchus is normal but the number of alveoli per acinus is increased 3 to 5 fold.

Left upper lobe is most commonly involved (42% of cases) followed by right upper lobe, right middle lobe right and left lower lobes. Infant may become symptomatic within few days after birth or may remain asymptomatic till months later. Earlier the onset of symptoms, more likely is the disease to be progressive.

Investigations

Chest X-ray

A large, hyperlucent lung with attenuated but defined vascularity is observed. Compressed remaining lung on that side, flattened hemidiaphragm, and widened intercostal spaces also are seen. An involved lung is seen herniated across the anterior midline. On a lateral view, the heart is displaced posteriorly with retrosternal lucency representing an anteriorly herniated lobe. The lobe is unchanged during exhalation or after placing the patient in the ipsilateral decubitus position. Chest fluoroscopy shows fixed lung and hemidiaphragm on the involved side. Radiographic appearance is characteristic of CLE and usually is not suggestive of other diagnoses.

CT Scan

CT scan shows a hyperlucent, hyper expanded lobe (attenuated but intact pattern of organized vascularity) with midline substernal lobar herniation and compression of the remaining lung. Usually, the mediastinum is significantly shifted away from the side of the abnormal lobe. *On antenatal ultrasound, it may appear as echogenic or cystic lesion which may decrease or show resolution in later antenatal ultrasound.*These cases should be followed up postnataly as the cystic changes reappear on postnatal chest radiographs and CT scans.

Diagnosis is usually not difficult but *CT and ventilation* perfusion scans may be helpful in determining whether surgical resection will be tolerated.

Additional diagnostic tests include:

- Xenon ventilation perfusion scintiscanning which shows delayed uptake and washout of isotope from air spaces and little blood flow in the emphysematous lobe.
- Bronchoscopy may reveal an aspirated foreign body, a mucus plug or an intrinsic obstruction.

- Echocardiography may be done when cardiac anomalies are suspected.
- MRI helps to diagnose an anomalous vessel compressing a bronchus.

Treatment

Not so long ago, surgical removal of the affected part of the lung was the standard treatment. However, after several reports advocated expectant management on the basis of a gradual resolution of symptoms in a number of cases, many pediatric pulmonologists will now tend towards a trial of supportive treatment and observation instead of resorting to surgery immediately after diagnosis.[9]

In case of observation, regular follow-up visits should be scheduled to ensure that pulmonary status does not worsen. Parents should be informed of the presence and potential complications of CLE. The presenting lobe may be the worst of a group of malacic bronchi, so even after definitive surgery, some children may continue with wheezing and prolonged expiratory phase with symptomatic additional small airway disease. Surgical intervention is indicated in cases with progressive pulmonary insufficiency. In very young infants with severe distress, segmental resection or lobectomy may be required as an emergency procedure. The ventilation required or anesthesia can produce sudden expansion of the affected lung resulting in abrupt cardiorespiratory failure. Thus, anesthesia must be coordinated so that thoracotomy can be done immediately. High-frequency jet ventilation should be considered in place of standard ventilatory techniques. Any thoracic cystic lesion expanding on chest radiography should be an indication for surgical resection, even if asymptomatic, because of the risk of pulmonary compression, infection, or malignant degeneration.

Flexible bronchoscopy with introduction of ultra thin bronchoscope into the bronchus of the affected lobe bronchus has been used to tide over the emergency situation in CLE with severe respiratory distress till child can be taken for surgery.

Long-term follow-up has shown no symptomatic functional impairment in these patients. The respiratory flow rates are diminished to 60-80 percent of normal.

Infants presenting with mild to moderate symptoms associated with normal bronchoscopic findings may be treated conservatively. Their ultimate pulmonary functions are equivalent to those of surgically treated patients. In conservative management, the patient should be under close follow up. In some cases the symptoms subside but the radiological abnormality persists.

In acquired forms, non-operative management can allow spontaneous resolution. The patient is usually in neonatal intensive care unit and often is on ventilation with close monitoring. Selective bronchial intubation may isolate the affected lung, thereby hastening resolution. Marraro *et al* have used bilumen endotracheal tube and two independent lung ventilators, for synchronized simultaneous independent lung ventilation in management of unilobar, unilateral, or multifocal lung disease.

High frequency oscillatory ventilation may be useful for treating severe acquired lobar emphysema.

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BRONCHOGENIC CYSTS[1-4]

Bronchogenic cysts may range from 1 to 10 cm in diameter, contain milky mucoid material and are lined by cuboidal or columnar ciliated epithelium and mucus glands. The cyst wall may have smooth muscle and cartilage. They may be located in the lung parenchyma, bronchial wall or in the mediastinum and can be single or multiple. It has also been reported in extrathoracic locations.

Clinical Features

More than two-thirds of patients present with symptoms. In the rest it is an incidental finding. It may present with pneumonia, or with severe respiratory distress without any obvious mass lesion in case of bronchial wall cyst. An infected cyst may sometimes be confused with a necrotizing lung abscess.

They are usually detected on chest X-ray and frequently *show an air-fluid level. CT chest is diagnostic.*

Pressure on trachea or bronchus may produce picture of lobar emphysema. Hemorrhage may also occur into the cyst. If left untreated it enlarges progressively compressing the adjacent structures, e.g. trachea, pulmonary vessels, esophagus or bronchi. Recurrent infections are common.

Adenocarcinoma and rhabdomyosarcomas originating in the cyst have been reported in the pediatric age group.[5,6]

Surgical Management

All bronchogenic cysts diagnosed in childhood should be excised because of risk of complications. Superficial cysts can be enucleated. Intraparenchymal cysts require segmentectomy or lobectomy.

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CONGENITAL CYSTIC ADENOMATOID MALFORMATION

Introduction

Congenital cystic adenomatoid malformation (CCAM) is an uncommon anomaly, characterized by an exaggerated adenomatoid overgrowth of the terminal bronchioles with consequent suppression of alveolar growth and the formation of intercommunicating cysts of variable sizes.[1,2] The routine use of antenatal ultrasound scanning has led to frequent antenatal diagnosis and has provided great insight into the natural history of CCAM. Improvements in surgical techniques (i.e. both antenatal and postnatal) as well as greatly enhanced imaging modalities have altered the surgical approach to this lesion.

Pathogenesis

CAM is believed to result from focal arrest in fetal lung development before the seventh week of gestation secondary to a variety of pulmonary insults. Depending on the time and type of insult, 4-26 percent of cases can be associated with other congenital abnormalities. However, arrest of pulmonary development with distortion of architectural differentiation may take place at any stage of embryonic development.

CAM differs from normal lung tissue because of a combination of increased cell proliferation and decreased apoptosis.[3] A well-defined intrapulmonary bronchial system is lacking, and normally formed bronchi supplying the mass are absent. In vitro work has focused attention on an imbalance between epithelial and mesenchymal growth on one hand and vascular development in lung tissue of children with CCAM on the other hand. Studies have suggested that an abnormal expression of glial cell–derived neurotrophic factor (GDNF) in epithelial and endothelial cells from CCAMs may mediate this imbalance during embyrogenesis.

Types of CAM

CAM is subdivided into 3 major types.[4]

Type I lesions, the most common, are composed of 1 or more cysts measuring 2-10 cm in diameter. Larger cysts are often accompanied by smaller cysts, and their walls contain muscle, elastic, or fibrous tissue. Cysts are frequently lined by pseudostratified columnar epithelial cells, which occasionally produce mucin. Mucinogenic differentiation is unique to this subtype of CAM.Type II lesions are characterized by small relatively uniform cysts resembling bronchioles. These cysts are lined by cuboid-to-columnar epithelium and have a thin fibro muscular wall. The cysts generally measure 0.5-2 cm in diameter.

Type III lesions consist of microscopic, adenomatoid cysts, and are grossly a solid mass without obvious cyst formation. Microscopic adenomatoid cysts are present.

Type II lesions are associated more frequently with other congenital malformations, while type III lesions are known to be associated with nonimmune fetal hydrops.

CAM receives its blood supply from the pulmonary circulation and is not sequestered from the tracheobronchial tree. However, type II and III lesions can occasionally coexist with extralobar sequestration, and in such cases, they may receive systemic arterial supply. CAM may also occur in combination with a polyalveolar lobe. A polyalveolar lobe is a form of congenital emphysema with increased number of alveoli with normal bronchi and pulmonary vasculature. CAM usually occurs early in fetal life, whereas polyalveolar lobe occurs late.

The other classification is based on the size of the cysts.[5]

a. **Microcystic** (cysts less than 5 mm in diameter)
b. **Mixed**
c. **Macrocystic** (cysts equal to or greater than 5 mm in diameter)

The condition is usually isolated. Unlike diaphragmatic hernia there is no association with chromosomal defects. In about 10 percent of cases there are additional malformations like renal abnormalities (bilateral renal agenesis), abdominal wall abnormalities, hydrocephalus, spinal deformities, gastrointestinal defects (diaphragmatic hernia, jejunal atresia, tracheoesophageal fistula), cardiac anomalies and anomalies of the great vessels (ventricular septal defect, tetralogy of Fallot, truncus arteriosus).

Clinical Features

With the increasing use of antenatal ultrasound as well as improvement in technology and skill, most cases of CCAM are diagnosed antenatally. Pregnancy usually is uneventful, other than the occasional complication of polyhydramnios. Most cases of CAM are diagnosed in the patient's first 6 months of life, with 70 percent of patients presenting in the first month of life. As many as 90 percent of cases are reported within the patient's first 2 years of life.[6] In the newborn period, patients with CCAM commonly present in the early neonatal period with progressive respiratory distress, and may die as a result. It may range in severity from grunting, tachypnea, and a mild oxygen requirement to fulminant respiratory failure requiring aggressive ventilator support or extra corporeal membrane oxygenation (ECMO). Multiple mechanisms account for the onset of respiratory difficulty. Pulmonary hypoplasia may arise as a consequence of a large CCAM, mediastinal shift may compromise cardiac and respiratory function, spontaneous pneumothoraces may occur, and air trapping within the cyst leads to compression of functional pulmonary tissue. Rarely, they may remain asymptomatic until mid- or late-childhood and then present with recurrent chest infections and pneumothorax. The importance of this needs to be emphasized as the presentation with recurrent chest infections will ultimately lead to more fibrotic changes in the lung tissues leading to diagnostic difficulties. They may rarely have pneumothorax and hemothorax as the presenting symptom.

There is a long term risk of malignant transformation.[7] Rhabdomyosarcoma, pulmonary blastomas, minute squamous cell carcinoma, and bronchioloalveolar carcinoma have all been described in association with CCAM.

Diagnosis

The diagnosis of CCAM is confirmed on radiology. Chest radiography is essential in the workup of the child with suspected CCAM. Chest radiography almost invariably identifies CCAM of sufficient size to cause clinical problems (Figs 31.2 and 31.3). The usual appearance is of a mass containing air-filled cysts with mediastinal shift.[8] The diagnosis may not be clear from chest radiography alone. Particularly in the case of type III lesions, chest radiography may demonstrate a mass without any evidence of cysts.

CT Scan Chest provides a safe and rapid means of defining the extent of CCAM in all age groups. The typical appearance is of multilocular cystic lesions

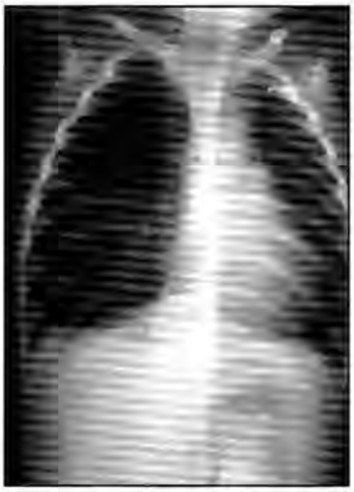

Fig. 31.2: Chest radiograph showing cystic adenomatoid malformation

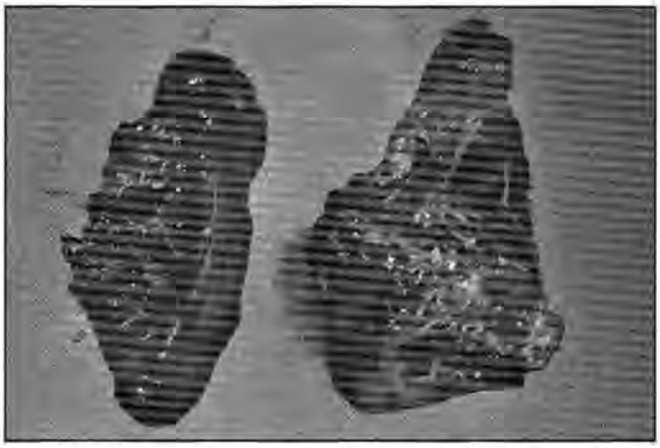

Fig. 31.3: Pathological specimen of lungs with cystic adenomatoid malformation *(For color version see Plate 7)*

with thin walls surrounded by normal lung parenchyma. It may also outline additional coexisting lesions. HRCT can differentiate between microcystic and macrocystic lesions with reasonable certainty.[9] CT scan has been shown to demonstrate lesions that have been completely resolved on the chest X-ray and Ultrasound. Overlapping CT features can exist among cases of CAM, pulmonary sequestration, bronchogenic cyst, and other foregut malformations; hence it may be difficult to differentiate among them on CT scan.

Prenatal Diagnosis: With increasing use and technical ability of antenatal ultrasonography, most cases of congenital lung anomalies are diagnosed prenatally. Ultrasound diagnosis is based on the finding of a solid or cystic, non-pulsatile intrathoracic tumor.[10] Common associated findings like polyhydramnios (65%), hydrops (common in microcystic form) and placentomegaly (in case of hydrops) can also be diagnosed. Unilateral lesions are often associated with deviation of the mediastinum in the contralateral side. In bilateral disease, the heart may be severely compressed, and this is usually associated with ascites from venocaval obstruction or cardiac compression. Lately the use of antenatal MRI is also being described.[11] MRI permits increased definition of a particular lesion, thereby enhancing the clinician's ability to accurately diagnose and offer an informed prognosis. When CAM is identified in utero, as many as 56 percent of the lesions detected can regress spontaneously.[12]

Treatment

Surgical intervention is the mainstay of therapy for CCAM. It consists of removal of the affected lobe (lobectomy). The management of completely asymptomatic patients is a controversial issue, but most authors advocate surgical resection as the treatment of choice for all cases of CAM because of the risk of pulmonary compression, infection or malignant transformation.[10] Recommendations for the timing of surgery range from early elective resection within the newborn period[13] to elective excision after 3 months.[14] The post-operative response is prompt in symptomatic patients.

Fetal surgery has evolved alongside the development of refinements in fetal imaging techniques. Surgery is an option for fetuses with life-threatening lesions such as the development of hydrops.[15] Of such patients, who have an anticipated mortality rate of nearly 100 percent, 60 percent can be saved with the resection of CAM. In patients with large multicystic lesions, resection of a lobe may be performed. In fetuses with a single dominant cyst, thoracoamniotic shunts have been placed. Absolute contraindications to fetal surgery include the presence of a significant chromosomal or structural anomaly, multiple pregnancies or maternal drug or nicotine abuse.[16] Children with respiratory distress might require intubation and ventilatory support. High frequency oscillatory technique avoids overexpansion of the cystic mass. Extracorporeal membrane oxygenation may be required in case of associated pulmonary hypertension and hypoplastic lung.

These patients, symptomatic or asymptomatic, require resection of affected lobe or lobes.

Prognosis

It primarily depends on the size of the lesion; larger lesions have a higher incidence of mediastinal shift and pulmonary hypoplasia and hence a worse prognosis.[17] Type III CAM tends to be extensive and therefore tends to have a poor prognosis. The prognosis is also poor with bilateral lung involvement, microcystic CCAM and severe associated malformations. The risk of mortality is 80-90 percent in fetuses with hydrops.

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ESOPHAGEAL ATRESIA AND TRACHEO-ESOPHAGEAL FISTULA (TEF)

This is a formidable problem that presents at birth. Once accurately and promptly diagnosed by the attending neonatologist/pediatrician, the baby should be transported to a tertiary care hospital. On other occasions an antenatal diagnosis allows the mother to be transported to a tertiary centres. The surgical results are good in centers with NICU (neonatal intensive care unit) facilities. The babies, who fare poorly are those who have other congenital abnormalities especially complex cardiac anomalies are low-birth weight and preterm.

Incidence

1:3000 to 1:4500 live births with male preponderance.

Associated Anomalies

At least 50 percent of infants with esophageal atresia have one of more associated anomalies. One of the common association is VACTERCL (V-Vertebral, A-Anorectal, C-cardiac, T-Trachea, E-esophageal, R-renal, L-limb). CHARGE is another syndrome (C-colobomo, H-Heart disease, A-atresia choanal, R-retardation (mental), G-genital hypoplasia, E-ear abnormalities).

Prognostic Classification

Three grades in increasing order of worse prognosis are as follows:
Waterston's 1962 classification

Group I Wt > 1500 gm – no major cardiac anomaly
Group II Wt > 1500 gm – or major cardiac anomaly
Group III Wt > 1500 gm – plus major cardiac anomaly

Current Staging

A Birth Wt > 2.5 kg
B Birth Wt 1.8-2.5 kg and moderate pneumonia or minor heart ailment
C Birth Wt > 1.8 kg with severe pneumonia and/or major heart ailment.

Diagnosis

Prenatal

95% cases	– Polyhydramnios in pure esophageal atresia
35% cases	– Polyhydramnios in esophageal atresia and distal tracheo esophageal fistula (TEF).

Postnatal

Failure to advance the tube beyond 10 cm indicates esopheal atresia. In the new born period there is drooling of saliva, inability to swallow, cyanotic episodes with/without attempt to feed and respiratory distress.

Investigations

A red rubber tube in the esophagus which usually does not go beyond 10 cm or curls up at the upper mediastinum is diagnostic of esophageal atresia. Usually nurse will report failure to pass the nasogastric tube in the patient with feeding problems/cyanosis on feeding/pooling of saliva. Air in the intestine suggests a tracheoesophageal fistula. The absence of intestinal gas suggest pure esophageal atresia. Contrast medium is usually not required.

As shown in the Figures 31.4 to 31.7 the most common being the esophageal atresia with distal TEF (Fig. 31.7) and the next being pure esophageal atresia (Fig. 31.4).

The H type TEF (Fig. 31.6) presents with choking, with every feed or epigastric distension due to the wide TEF. The key to a good result with H type is an accurate diagonsis. Barium paste is used to outline the fistula which is N or Z type. Sometimes a

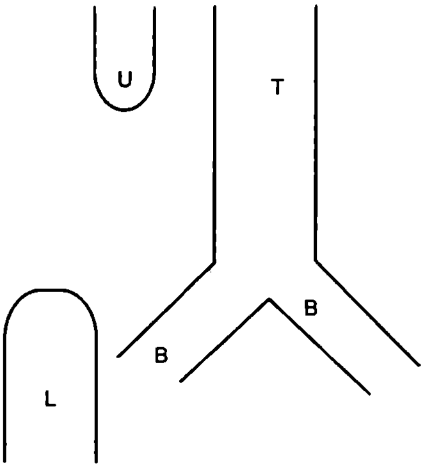

Fig. 31.4: Pure esophageal atresia. No fistula

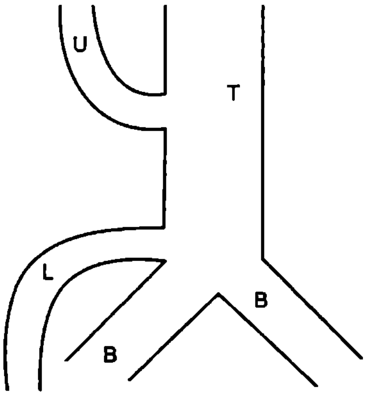

Fig. 31.5: Proximal and distal tracheo esophageal fistula

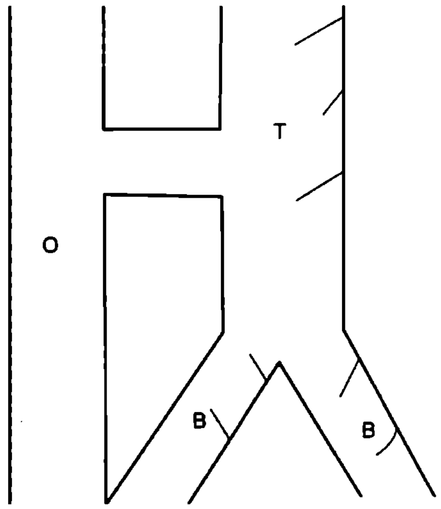

Fig. 31.6: H-type TEF no esophageal atresia or stenosis

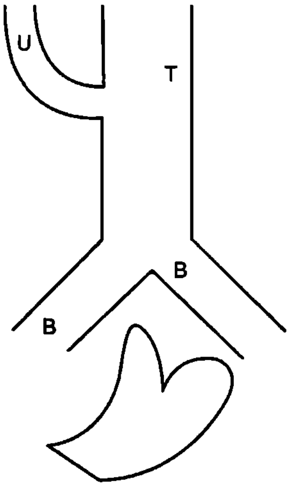

Fig. 31.7: Upper pouch tracheoesophageal fistula

bronchoscopy with esophagoscopy is required, superiorly trachea and inferiorly esophagus. Surgical division is easy and result is very good, if the diagnosis is accurate.

Management

Emergency surgery in the middle of the night was the norm rather than the exception in the past but at present elective emergency surgery the next morning is the current planning. This enables us to evaluate the baby for associated anomalies. The upper pouch is kept empty by the use of Replogle tube or oral suction to avoid aspiration pneumonia. Some neonates may require ventilatory support. In our circumstances where neonates with esophageal atresia may go undetected, initial management with antibiotics and respiratory support may be necessary.

Surgical Management

- Primary repair of esophagus
- Ligation of tracheoesophageal fistula
- Gastrostomy
- Esophagostomy

The primary aim is to bring the native esophagus together. However, in a pure esophageal atresia it is often difficult to do a primary repair. A gastrostomy is done to enable feeding. A esophagostomy may be done and sham feeding started. However, where a NICU exists the upper esophagus may be kept empty by oral suction and serial evaluation of the gap between the upper and lower pouch done using Bake's dilators and a primary repair attempted at 8-12 weeks.

In case the baby has severe infection or/and inability to maintain oxygen saturations the tracheoesophageal fistula must be ligated and the repair of the esophagus may be undertaken later. If the esophageal anostomosis is tight, elective ventilaton is undertaken for 4 to 6 days. In case an esophagostomy and gastrostomy is done then esophageal replacement has to be planned.

A right thoracotomy and division of the azygos is usually done except when there is a right aortic arch. An extra pleural approach is preferred. With thoracoscopy, the approach is necessarily intrapleural.

PICU/NICU Problems

Preoperative

Feeding in an undiagnosed baby with esophageal atresia leads to pneumonia and consequently increases the morbidity and mortality.

Pooling of saliva in the upper pouch if not adequately nursed can lead right upper lobe collapse and pneumonia.

Surgical and Postoperative Complications

Surgical and postoperative complications include injury to the recurrent laryngeal nerve especially in H-type TEF. Other problems that the intensivist needs to be aware of requiring intensive care management with or without mechanical ventilation. In the immediate postoperative period one may encounter Anastomotic Leakage, Pneumothorax Thoracic Infection (Mediastinitis), Pneumonitis, Sepsis. Conservative management with intravenous antibiotics suchy as cefotaxime/ metrogyl may be sufficient. If there is respiratory distress/pneumothorax, a tube thoracostomy with or without ventilation may be required, until stability is achieved. A repeat surgical option may be considered for persistent leak.

Long-term Complications may include:

- Esophageal stenosis
- Complications relating to esophageal replacement
- Recurrent tracheoesophageal fistula
- Gastroesophageal reflux
- Dysphagia
- Tracheomalacia

FURTHER READING

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CHAPTER

Bronchodilator Therapy in Mechanically Ventilated Children

Rajesh Chawla, Praveen Khilnani

Drugs particularly bronchodilator has been delivered into the lung through the airway for many years, yet information regarding their efficacy and the optimal technique for their administration has been limited. Inhaled drugs are preferred because of obvious reasons such as rapid onset of action, smaller dose requirement, drug delivery directly into the airways and side minimal effects are much less.[1,2] *If proper technique is used it is now possible to deliver inhaled drugs safely, conveniently and effectively in mechanically ventilated infants, children and adults.*

Principles of Aerosol Therapy

The delivery of aerosols to the airways is determined by the following factors.

Particle Size

Most important aspect of aerosol deposition is the particle size. Medical aerosols are heterodisperse. The particle diameter in the aerosol is expressed as Median Aerodynamic Diameter (MAD). It is the particle size (expressed in microns) at which half of the mass of particles in the aerosol are less and half are greater than MAD. Nebulizers and metered dose inhalers are commonly used for aerosol therapy and they produce respirable particle with a MMAD between 1 to 5 microns. The larger particles than 5 microns are deposited in the major airways.

Impaction

The impaction of particles is dependent on the particle size as well as on the velocity of airflow. If the velocity of airflow is high even the smallest particles have tendency to get deposited in the larger airways because of high velocity and inertia.

If the inspiratory flow is more than 30 L/minute, particles larger than 2 microns can get deposited in larger airways.

Sedimentation

The greater the mass of the particle the faster it will settle down. If an ambulatory patient holds his breath for 4-10 seconds the small particle will also settle down by gravitational sedimentation in the last 6 generations of the airways.

Diffusion

As the aerosol reaches the lung parenchyma, the flow and inertia of the particle is reduced to zero. Aerosol particles collide with other particles and deposit upon contact with the airway surface. Particles of less than 1 micron are so small and light that most of them are exhaled.[3] Aerosol droplet with size between 1-5 microns have better chance of deposition in the major airways.

Devices Used for Aerosol Therapy during Mechanical Ventilation

There are mainly two types of devices which have been used for aerosol therapy during the mechanical ventilation.

1. Nebulizer
2. Metered dose inhaler (MDI) with adapter

Nebulizers

During mechanical ventilation, a device such as a nebulizer produces aerosol particles with MAD of 1-3 microns, which are more likely to achieve deposition in the lower respiratory tract.[4] Particles larger than 3 microns get deposited in the ventilator circuit and endotracheal tube.

Nebulization can be given by two ways to a ventilated patient.

a. A nebulizer unit, powered by pressurized gas from a piped wall system, oxygen cylinder or compressor which is interposed in the inspiratory limb of the ventilator circuit.
b. Nebulizer can be powered by airflow generated by ventilator during inspiration intermittently.

A separate line provides airflow from the ventilator to a nebulizer connected in the ventilator circuit. However the major drawback of this technique is that the driving pressure provided by most ventilators is lower than the one provided by a separate oxygen source supply or by compressed air. The decreased flow reduces the efficiency of pneumatic nebulizer and increases MMAD of the aerosol. This will result in reducing the delivery of aerosol to the lower respiratory tract.

Metered Dose Inhalers (MDI)

Initially there was great concern regarding connecting MDI to the ventilator circuit. Now it is possible to attach MDI with adapters which can be attached directly to the endotracheal tube or within line device that are placed in the inspiratory limb of the ventilatory circuit. These include chamber adapters such as cylindrical spacers and reservoir devices. There are various factors, which determine the deposition of aerosol delivered by MDI in mechanically ventilated patients.

Factors Affecting Delivery of Aerosol Particles during Mechanical Ventilation

Ventilatory Parameters

The delivery of aerosol is dependent on the following ventilatory parameters:

1. *Mode of ventilation*: The aerosol deposition is 23 percent higher with stimulated spontaneous breath (CPAP) than with controlled breath. Usually control/assist control or pressure support mode is used.
2. *Tidal volume*: Tidal volume delivered in each breath must be larger than the volume of ventilator tubing and endotracheal tube. Higher tidal volume is associated with increased aerosol delivery.
3. *Inspiratory time*: The larger the inspiratory time, greater is the deposition of aerosol.
4. Duty Cycle–(Ti/Ttot) Ratio of inspiratory time (Ti) to total breath cycle time (Ttot)—Because nebulizer generates aerosol over several minutes, longer Ti has cumulative effect in improving aerosol delivery.[5,6]
5. *Wave-forms*: During mechanical ventilation, square wave forms with considerable high flow rate influence and decrease delivery of aerosol to the lower respiratory tract.

Ventilator Circuit

The deposition in the airways is also determined by the configuration of ventilatory circuit.

1. *Endotracheal tube size*: The narrower the tube size, less is the delivery of aerosol into the lower respiratory tract. In children with ET tube size 6 to 3 mm, the efficiency of aerosol delivery is significantly reduced.[7]
2. *Humidification of inspired gas*: This reduces the aerosol delivery by 40 percent. This can be overcome by two ways:[6,8,9]
   i. Omit humidifier and give nebulization without the humidifier. This may result in drying of the airways.
   ii. Retain humidifier but increase the dose of nebulized medication. This is the preferred method.

Device Related Factors

1. *MDI with spacer* There are three important factors, which determine aerosol delivery are:
   a. Type of spacer or adapter used.
   b. Position of spacer in the circuit
   c. Timing of the MDI actuation[10,11]
2. *Nebulizer*
   a. *Type of nebulizer* Nebulizer performance varies with the diluent volume, gas flow, and operating pressure and nebulizer model. When the gas flow driving the nebulizer is from a

secondary gas source other than the ventilator, the volume, flows and pressure delivered by ventilator to the patient are altered.

b. *Position in the circuit* If placed at least 30 cm from the proximal end of endotracheal tube, the delivery of aerosol is better in adult circuits.

Patient Related Factors

1. Severity of airway obstruction. More severe the obstruction the less will be the delivered aerosol.
2. Mechanism of airway obstruction.
3. Patient ventilator synchrony.

Assessment of Lower Respiratory Tract Aerosol Deposition in vivo

There are two ways by which aerosol deposition in the airways can be assessed.

a. Radionuclide studies.
b. Estimation of Plasma level can be used.

Comparison of Aerosol Administration between MDI and Nebulizer in Mechanically Ventilated Patient

The technique of aerosol administration often requires a compromise between the optimal operating characteristics of the aerosol generator and the patient's pulmonary mechanics. For example, a longer duty cycle (Ti/Ttot) increases aerosol deposition in the lung, but it may worsen dynamic hyperinflation in patients with air flow limitation.

Review of some of the data on administration techniques shows that the best delivery with a nebulizer during CMV (15%) was accomplished using a speciality nebulizer (Aero Tech 11, CIS-US Inc, Bedford, MA) that produces an MMAD of <2 microns (requiring 35 min to administer), in a dry ventilator circuit, with a duty cycle of 0.5. This technique achieves optimal aerosol deposition but may be difficult for the patient to tolerate. Use of a commonly available nebulizer that produces aerosols with 3.5 microns MAD takes half the time but may reduce the dose delivered to the lung by half and the deposition to 7.5 percent. Providing active humidity during aerosol administration reduces delivery by another 40 percent (to 4%), as would reducing duty cycle to a more common 0.25 (reducing deposition to 2%). The impact of each of these variables on aerosol delivery could explain the differences between 15 percent of the nominal dose being delivered under optimal conditions and the more commonly reported 2 percent delivery. Thus, 50 micrograms of Salbutamol would be delivered to the lung with a nominal dose of 2.5 mg with a nebulizer. This dose would be similar to the 60 microgram of Salbutamol delivered from 4 puffs of an MDI with chamber adapter in humidi-fied circuit (15% deposition). Hence the effectiveness of MDI and nebulizer is similar.

Technique for Using Nebulizer in Mechanically Ventilated Patients[12]

1. Place drug solution in nebulizer to optimal fill volume (2-6 ml).
2. Place nebulizer in inspiratory line at least 30 cm from the patient endotracheal tube.
3. Ensure airflow of 6-8 L/min through the nebulizer.
4. Ensure adequate tidal volume (> 500 ml in adults and 10-15 ml/kg in children). Attempts to use duty cycle > 0.3, if possible.
5. Adjust minute volume, sensitivity trigger, and alarms to compensate for additional air flow through the nebulizer, if required.
6. Observe nebulizer for adequate aerosol generation throughout its use.
7. Disconnect nebulizer when all medication is nebulized or when no more aerosols are being produced. Store nebulizer under aseptic conditions.
8. Reconnect ventilator circuit and return to original ventilator and alarm settings.

Technique for Using MDI in Mechanically Ventilated Patients[12]

1. Assure tidal volume > 500 ml (in adults and 10-15 ml/kg in children) during assisted ventilation.
2. Aim for an inspiratory time (excluding the inspiratory pause) > 0.3 of total breath duration.
3. Ensure that the ventilator breath is synchronized with the patient's inspiration.
4. Shake the MDI vigorously.
5. Place canister in actuator of a cylindrical spacer situated in inspiratory limb of ventilator circuit.
6. Actuate MDI to synchronize with precise onset of inspiration by the ventilator.
7. Allow passive exhalation.
8. Repeat after 20-30 seconds.

Indication and Efficacy of Bronchodilator Therapy

The presence of one or more of the following in the mechanically ventilated patient suggests the need for bronchodilator administration.

1. Previously demonstrated response to bronchodilator.
2. Presence of auto-PEEP not eliminated by reduced respiratory rate, increased inspiratory flow or decreased 1:E ratio.
3. Increased airway resistance as evidenced by:
    a. Increased difference between peak pressure and plateau pressure.
    b. Wheezing or decreased breath sounds.
    c. Intercostal and or sternal retractions.
    d. Persistent use of spacers and nebulizers.

The centers for disease control and prevention recommended that nebulizer should be sterilized at the start of nebulization and after each use. Nebulizers should be removed from the ventilator circuit, disassembled, cleared with sterile water rinsed and air dried. Care should also be taken to sterilize them.

In addition single dose ampules are preferred. If using multidose vial, discard it after every 24 hours.

Use a spacer chamber to actuate an MDI. The spacer diameter should be removed from the ventilator circuit between treatments.

Drugs Used for Bronchodilator and Dose

1. Salbutamol 0.5 percent solution 5 mg/ml (continuously 5 to 15 mg/hour in a PICU with close monitoring of heart rate) 0.01-0.03 ml/kg max unit dose 5 mg in 2.5 ml normal saline every 4 to 6 hours.
2. Terbutaline 1 percent solution 10 mg/ml, 0.03 ml/kg (max 10 mg or 1 ml diluted with 1.5 ml normal saline every 4 to 6 hours.
3. Fenoterol.
4. Ipratropium bromide: 20-40 microgram metered dose nebulized 250 microgram unit dose.
5. Isoetharine (bronkosol) 0.01 ml/kg. 0.25-0.5 ml (3-5 mg) of 1 percent (10 mg/ml) solution in 2.5 ml normal saline.

All produce significant bronchodilation.

Doses of drugs are given in optimal conditions. If the conditions are suboptimal higher doses may be required. In general no serious side effects have been reported other than tachycardias and restlessness. As a word of caution, excessive pressure build up in the circuit should be avoided by setting high pressure alarm and pressure pop off in the ventilator to prevent baro/volutrauma related problems. The risk of hypokalemia is increased with high doses.

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CHAPTER

Basic Mechanical Ventilation

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INTRODUCTION

Mechanical ventilation in children and neonates is different from adults.

While basic priciples of physics and gas flow apply to all age groups, anatomical and physiological differences play a significant role in selecting the type of ventilator as well as the ventilatory modes and settings.

Upper airway in children is cephalad, funnel shaped with narrowest area being subglottic (at the level of cricoid ring), as compared to adults where the upper airway is tubular with narrowest part at the vocal cords.[1] Airway resistance increases inversely by 4th power of radius; i.e.in an already small airway even one mm of edema or secretions will increase the airway resistance and turbulent flow markedly necessitating treatment of airway edema, suctioning of secretion, measures to control secretions. Low functional residual capacity (FRC :Volume of air in the lungs at end of expiration) reduces the oxygen reserve, reduces the time that apnea can be allowed in a child.

Respirations are shallow and rapid due to predominant diaphragmatic breathing, and inadequate chest expansion due to inadequate costovertebral bucket handle movement in children. Therefore a child tends to get tachypneic rather than increasing the depth of respiration in response to hypoxemia. Oxygen consumption/kg body weight is higher therefore tolerance to hypoxemia is lower.

Susceptibility to bradycardia in response to hypoxemia is also higher due to high vagal tone. Pores of Kohn and channels of Lambert (brocho alveolar and interalveolar collaterals) are inadequately developed making regional atelectasis more frequent.[2] Closing volumes are lower and airway collapse due to inadequate strength of the cartilage in the airways is common making a child particularly susceptible to laryngomalacia, and tracheobronchomalacia as well as lower airways closure.

Therefore, children tend to require smaller tidal volumes, faster respiratory rates, adequate size uncuffed endotrachel tube, adequately suctioned clear airway for proper management of mechanical ventilation. Other important factors for chosing the ventilatory setting include the primary pathology, i.e. asthma, ARDS, pneumonia, airleak syndrome raised intracranial tension, neuromuscular weakness, neonatal hyaline membrane disease, or neonatal persistent pulmonary hypertension (PPHN).

Basic Physiology[3]

Gradient between mouth and pleural space is the driving pressure for the inspired gases, and this gradient is needed to overcome resistance and to maintain alveolus open, by overcoming elastic recoil forces.

Therefore, a balance between elastic recoil of chest wall and the lung determines lung volume at any given time. Normal inspiration is actively initiated by negative intrathoracic pressure driving air into the lungs. Expiration is passive.

Ventilation

Ventilation washes out carbon dioxide from alveoli keeping arterial $PaCO_2$ between 35-45 mm of Hg. Increasing dead space increases the $PaCO_2$.

$$PaCO_2 = k \times \frac{\text{Metabolic production}}{\text{Alveolar minute ventilation}}$$

Alveolar MV = respiratory rate x effective tidal volume
Effective TV = TV – dead space
Dead Space = Anatomic (nose, pharynx, trachea, bronchi) + Physiologic (alveoli that are ventilated but not perfused)

Adequate minute ventilation is essential to keep $PaCO_2$ within normal limits.

Oxygenation

Partial pressure of oxygen in alveolus (PAO_2) is the driving pressure for gas exchange across the alveolar-capillary barrier determining oxygenation.
$PAO_2 = (\{\text{Atmospheric pressure} - \text{water vapor}\} \times FiO_2) - PaCO_2/RQ$
RQ = respiratory quotient

Adequate perfusion to alveoli that are well ventilated improves oxygenation.

Hemoglobin is fully saturated 1/3 of the way through the capillary.

Hypoxemia can occur due to:
a. Hypoventilation
b. V/Q mismatch(V- ventilation,Q- perfusion)
c. Shunt(Perfusion of an unventilated alveolus, atelectasis, fluid in the alveous)
d. Diffusion impairments

Hypercarbia can occur due to:
a. Hypoventilation
b. V/Q mismatch
c. Dead space ventilation

Gas Exchange

Hypoventilation and V/Q mismatch are the most common causes of abnormal gas exchange in the PICU.

One can correct hypoventilation by increasing minute ventilation.

One can correct V/Q mismatch by increasing amount of lung that is ventilated or by improving perfusion to those areas that are ventilated.

Time Constant

Time constant is the time required to fill an alveolar space. It depends on the resistance and compliance.In pediatric age group one time constant that fills an alveolar unit to 63 percent of its capacity is 0.15 seconds. It takes three time constants to achieve greater than 90 percent capacity of the alveolar unit filled.

Time constant = Resistance x Compliance

This signifies that a certain minimum inspiratory time is required to fill the alveoli adequately which is generally two to three time constants; i.e. 0.3 to 0.45 seconds.This is important when selecting the inspiratory time on the conventional ventilator.

Indications of Mechanical Ventilation[4] (Flow chart 33.1)

Indications remain essentially clinical may not be always substantiated by objective lab parameters such as blood gas analysis.
Common indications include:

1. Respiratory Failure
   a. Apnea/Respiratory Arrest
   b. Inadequate ventilation
   c. Inadequate oxygenation
   d. Chronic respiratory insufficiency with failure to thrive
2. Cardiac Insufficiency/Shock
   a. Eliminate work of breathing
   b. Reduce oxygen consumption
3. Neurologic dysfunction
   a. Central hypoventilation/frequent apnea
   b. Patient comatose, GCS (Glasgow Coma Score) ≤ 8
   c. Inability to protect airway

Commonly used Nomenclature

Airway pressures
Peak inspiratory pressure (PIP)
Positive end expiratory pressure (PEEP)
Pressure above peep (PAP)
Mean airway pressure (MAP)

Continuous Positive Airway Pressure (CPAP)

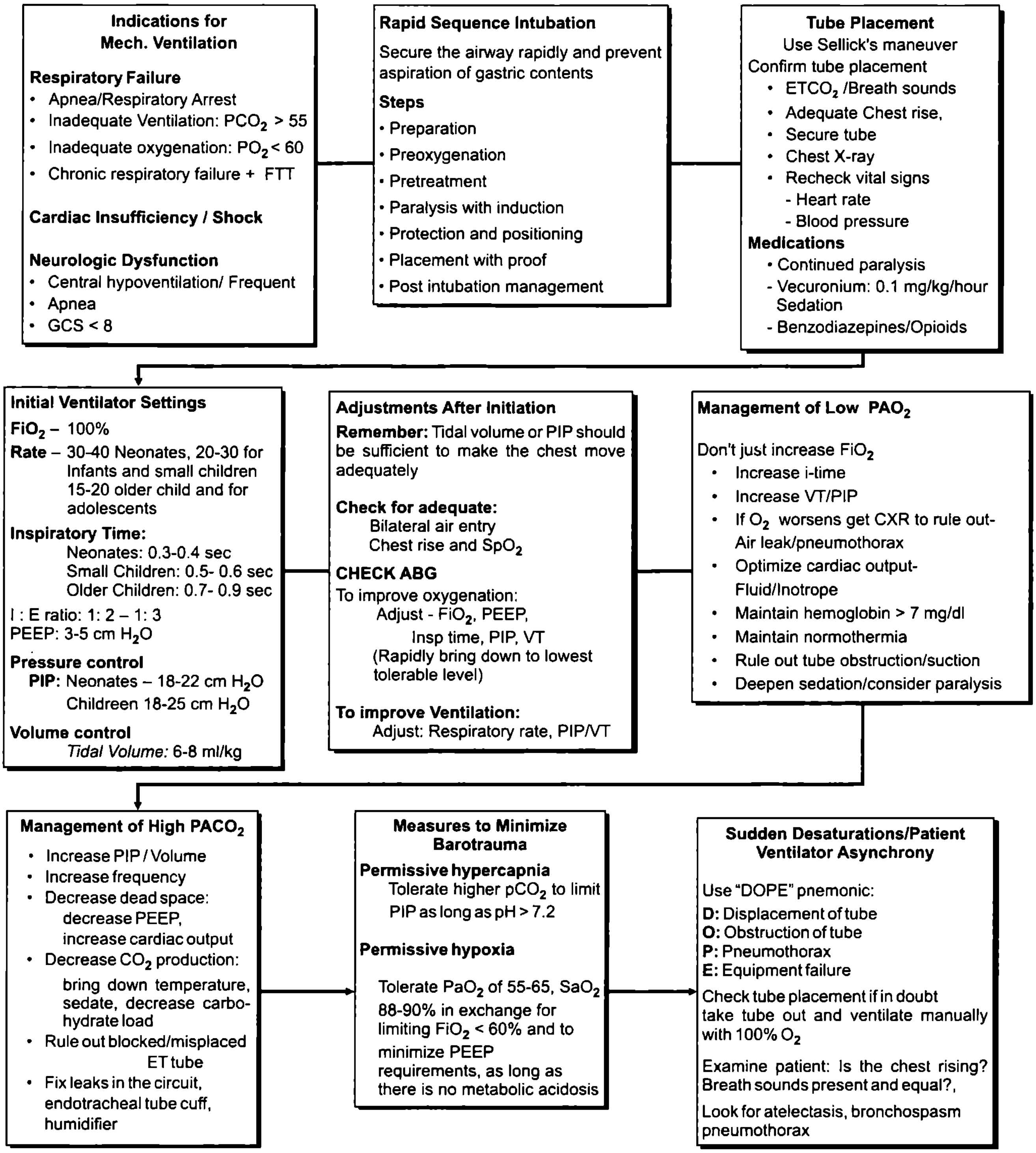
Inspiratory time or I:E ratio,
Frequency(f):Ventilatory rate
Tidal volume(Vt): Amount of gas delivered with each breath

Modes of Ventilation

Control Modes

In this mode every breath is fully supported by the ventilator. In classic control modes, patients were

Flow chart 33.1: Basic mechanical ventilation



Indications for Mech. Ventilation

Respiratory Failure
- Apnea/Respiratory Arrest
- Inadequate Ventilation: $PCO_2 > 55$
- Inadequate oxygenation: $PO_2 < 60$
- Chronic respiratory failure + FTT

Cardiac Insufficiency / Shock

Neurologic Dysfunction
- Central hypoventilation/ Frequent
- Apnea
- GCS < 8

Rapid Sequence Intubation

Secure the airway rapidly and prevent aspiration of gastric contents

Steps
- Preparation
- Preoxygenation
- Pretreatment
- Paralysis with induction
- Protection and positioning
- Placement with proof
- Post intubation management

Tube Placement

Use Sellick's maneuver

Confirm tube placement
- $ETCO_2$ /Breath sounds
- Adequate Chest rise,
- Secure tube
- Chest X-ray
- Recheck vital signs
  - Heart rate
  - Blood pressure

Medications
- Continued paralysis
- Vecuronium: 0.1 mg/kg/hour

Sedation
- Benzodiazepines/Opioids

Initial Ventilator Settings

FiO_2 – 100%

Rate – 30-40 Neonates, 20-30 for Infants and small children 15-20 older child and for adolescents

Inspiratory Time:
Neonates: 0.3-0.4 sec
Small Children: 0.5- 0.6 sec
Older Children: 0.7- 0.9 sec

I : E ratio: 1: 2 – 1: 3
PEEP: 3-5 cm H_2O

Pressure control
PIP: Neonates – 18-22 cm H_2O
Childreen 18-25 cm H_2O

Volume control
Tidal Volume: 6-8 ml/kg

Adjustments After Initiation

Remember: Tidal volume or PIP should be sufficient to make the chest move adequately

Check for adequate:
Bilateral air entry
Chest rise and SpO_2

CHECK ABG

To improve oxygenation:
Adjust - FiO_2, PEEP,
Insp time, PIP, VT
(Rapidly bring down to lowest tolerable level)

To improve Ventilation:
Adjust: Respiratory rate, PIP/VT

Management of Low PAO_2

Don't just increase FiO_2
- Increase i-time
- Increase VT/PIP
- If O_2 worsens get CXR to rule out-Air leak/pneumothorax
- Optimize cardiac output-Fluid/Inotrope
- Maintain hemoglobin > 7 mg/dl
- Maintain normothermia
- Rule out tube obstruction/suction
- Deepen sedation/consider paralysis

Management of High $PACO_2$
- Increase PIP / Volume
- Increase frequency
- Decrease dead space: decrease PEEP, increase cardiac output
- Decrease CO_2 production: bring down temperature, sedate, decrease carbohydrate load
- Rule out blocked/misplaced ET tube
- Fix leaks in the circuit, endotracheal tube cuff, humidifier

Measures to Minimize Barotrauma

Permissive hypercapnia
Tolerate higher pCO_2 to limit PIP as long as pH > 7.2

Permissive hypoxia

Tolerate PaO_2 of 55-65, SaO_2 88-90% in exchange for limiting $FiO_2 < 60\%$ and to minimize PEEP requirements, as long as there is no metabolic acidosis

Sudden Desaturations/Patient Ventilator Asynchrony

Use "DOPE" pnemonic:
D: Displacement of tube
O: Obstruction of tube
P: Pneumothorax
E: Equipment failure

Check tube placement if in doubt take tube out and ventilate manually with 100% O_2

Examine patient: Is the chest rising? Breath sounds present and equal?,

Look for atelectasis, bronchospasm pneumothorax

(PIP: Peak inspiratory pressure, PCO_2: Partial pressure of CO_2, PaO_2: Partial pressure of oxygen, $ETCO_2$ end tidal CO_2 FTT: Failure to thrive, SaO_2 arterial oxygen saturation) unable to breathe except at the controlled set rate. In a conventional controlled mode, weaning is not possible by decreasing rate, patient may hyperventilate if agitated leading to patient/ventilator asynchrony. Patients on control modes will need sedation and or paralysis with a muscle relaxant. In newer control modes, machines may act in assist-control, with a minimum set rate and all triggered breaths above that rate are also fully supported.

IMV Modes

Intermittent mandatory ventilation modes. In this mode breaths "above" set rate are not supported. Most modern ventilators have synchronized intermittent mandatory ventilation (SIMV)

SIMV: Ventilator Synchronizes IMV "Breath" with Patient's Effort

Patient takes "own" breaths in between (with or without pressure support) the set SIMV rate.There is a potential for increased work of breathing and patient/ventilator asynchrony, if the trigger sensitivity set on the ventilator is too low requiring patient to generate higher negative inspiratory force to trigger a supported breath.

Support Mode

Pressure Support[5]

Ventilator supplies pressure support (flow) at a preset level but rate is determined by the patient, expiration begins passively when inspiratory flow decreases below a certain level preset in the ventilator (flow cycled); Volume support is also available in Servo 300 ventilators following the principle of pressure suport delivery of the set volume over the patients natural inspiratory time duration keeping the pressure to a minimum.

Pressure support can decrease work of breathing by providing flow during inspiration for patient triggered breaths. It can be given with spontaneous breaths in IMV modes or as stand alone mode without set rate, as well as for weaning to retrain coordination of respiratory muscles in patients on ventilation for longer than few weeks.

BASIC FUNDAMENTALS OF VENTILATION

Ventilators deliver gas to the lungs using positive pressure at a certain rate. The amount of gas delivered can be *limited* by time, pressure or volume. The duration can be *cycled* by time, pressure or flow.

If volume is set, pressure varies; if pressure is set, volume varies according to the compliance.

Compliance = $D_{volume}/D_{pressure}$

Chest must rise no matter which mode is chosen

Following are three main expectations from the ventilator:

1. Ventilator must recognize patient's respiratory efforts (trigger)
2. Ventilator must be able to meet patient's demands (response)
3. Ventilator must not interfere with patient's efforts (synchrony)

Whenever a breath is supported by the ventilator, regardless of the mode, the limit of the support is determined by a preset pressure or volume.

Volume limited: Preset tidal volume

Pressure limited: Preset PIP

Pressure vs Volume Control[6]

Goal is to ventilate and oxygenate adequately. Both pressure and volume control modes can achieve it. Important requirements include adequate movement of the chest and minimal barotrauma or volutrauma.

One must have a set up of high/low pressure alarms in volume cycling and, low expired tidal volume alarm when using pressure cycling.

Pressure Limited Ventilation (Fig. 33.1)

Ventilator stops the inspiratory cycle when set PIP is achieved.

Caution: Tidal volume changes suddenly as patient's compliance changes. Ventilator delivers a decelerating flow pattern (lower PIP for same Vt)

This can lead to hypoventilation or overexpansion of the lung.

If endotracheal tube is obstructed acutely, delivered tidal volume will decrease. This mode is useful if there is a leak around the endotracheal tube.

For improving oxygenation,one needs to control FiO_2 and MAP, (I-time, PIP, PEEP) and to influence ventilation, one needs to control PIP and respiratory rate.

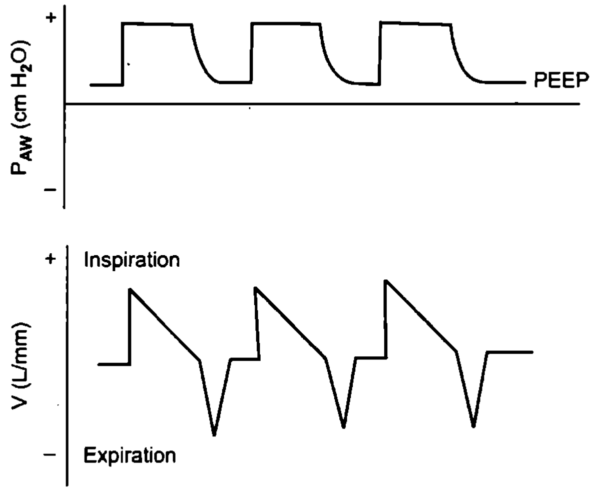


Fig. 33.1: Pressure control ventilation. The ventilator delivers breaths with a preset inspiratory pressure and decelerating flow

Volume Limited Ventilation (Fig. 33.2)

Ventilator stops the inspiratory cycle when set tidal volume has been delivered.

One can control minute ventilation by changing the tidal volume and rate. For improving oxygenation primarily FiO_2, PEEP, I-time can be manipulated. Increasing tidal volume will also increase the PIP, hence affecting the oxygenation by increasing the mean airway pressure. It delivers volume in a square wave flow pattern. Square wave(constant) flow pattern results in higher PIP for same tidal volume as compared to pressure modes.

Caution: There is no limit *per se* on PIP (so ventilator alarm will have to be set for an upper pressure limit to avoid barotrauma). Volume is lost if there is a circuit leak or significant leak around the endotracheal tube, therefore an expired tidal volume needs to be monitored and set. Some ventilators will alarm automatically if the difference between set inspired tidal volume and expired tidal volume is significant (varies between the ventilators).

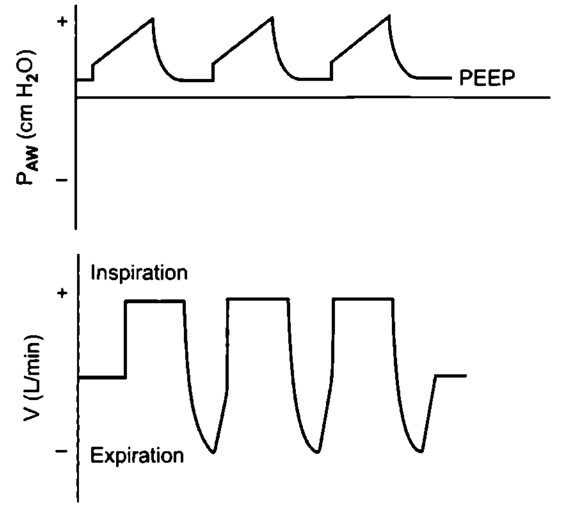


Fig. 33.2: Volume control ventilation. The ventilator delivers the preset tidal vomume at a constant flow rate

Trigger/Sensitivity

Trigger means sensitivity setting of the ventilator. ventilators have a negative pressure sensor which can be set at various levels of sensitivity to initiate a breath usually based on patient effort(negative pressure) or elapsed time before the next breath in the event of respiratory depression or apnea. The patient's effort can be "sensed" as a change in pressure or a change in flow in the circuit (flow triggering). A setting of greater than 0 makes it too sensitive (meaning the triggered breath from the ventilator will be too frequent). A negative setting (negativel or negative 2) setting is usually acceptable. Too negative setting will increase the work of the patient (to generate a negative pressure) to trigger a ventilator breath.

Advanced Modes

Pressure-regulated volume control (PRVC)
Volume support
Inverse ratio (IRV) or airway-pressure release ventilation (APRV)
Bilevel positive airway pressure(BIPAP)
High-frequency ventilation/Oscillation

Pressure Regulated Volume Control (PRVC)[7] *(Fig. 33.3)*

It is essentially a control mode, which delivers a set tidal volume with each breath at the lowest possible peak pressure. It delivers the breath with a decelerating flow pattern that is thought to be less injurious to the lung.

Volume support: Volume support is in principle equivalent to pressure support where a "goal" tidal volume is set and machine delivers that volume at variable pressure support, but within the set limits of pressure support. The machine watches the delivered volumes and adjusts the pressure support to meet desired "goal" within limits set.

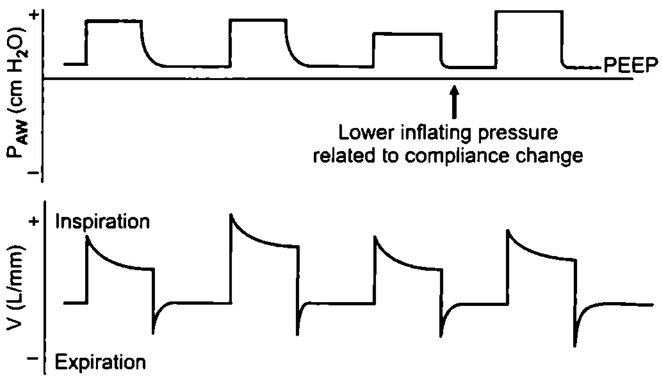


Fig. 33.3: Prssure-regulated volume control. Breaths are delivered at the lowest possible inflating pressure to deliver the preset tidal volume according to the dynamic changes in lung-thorax machanical properties. The pressure is kept constant and inspiratory flow is decelerating

Other advanced modes are beyond the scope of this discussion.

Initial Ventilator Settings

One should always have the general idea regarding what initial ventilatory settings to choose when initiating the ventilation. Parameters to choose include:

Rate: start with a rate that is somewhat normal, i.e. 15 for adolescent/child, 20-30 for infant/small child, 30-40 for a neonate.

FiO_2: 1(100 percent) and wean down to level<0.5.

PEEP: 3-5 cm of H_2O (higher if ARDS, low compliance disease, lower if Asthma, high compliance disease.

Inspiratory time (I-time or I:E ratio): 0.3 to 0.4 sec for neonates, 0.5-0.6 sec for children, 0.7-0.9 in older children. Normal I:E ratio = 1:2-1:3

Higher I-times may be needed to improve oxygenation in difficult situations (Inverse ratio ventilation) increasing the risk of air leak.

Choose the Mode

Pressure Limited

PIP is set depending upon lung compliance and pathology.
Neonates 18-22 cm H_2O
Children 18-25 cm H_2O

Volume Limited

Tidal volume 8 ml/kg.

Adjustments after Initiation

Usually based on blood gases and oxygen saturations

For oxygenation FiO_2, PEEP, i time, PIP (Tidal volume) can be adjusted (increase MAP).

For ventilation Respiratory rate, Tidal volume (in volume limited) and PIP (In pressure limited mode) can be adjusted.

PEEP is used to help prevent alveolar collapse at end inspiration; it can also be used to recruit collapsed lung spaces or to stent open floppy airways.

Gas Exchange Related Problems

Inadequate Oxygenation (Hypoxemia)
Inadequate Ventilation (Hypercarbia)

Inadequate Oxygenation

Important guidelines

1. Don't just increase FiO_2
2. Increase tidal volume if volume limited mode, PEEP, Inspiratory time (↑ MAP) (Fig. 33.4).
3. Increase peak inspiratory pressure(pip)/peep/inspiratory time (ti) if pressure limited mode (↑ MAP).
4. If O_2 worse, get chest X-ray to rule out air leak(treat!)/if lung fields show worsening (increase PEEP further).

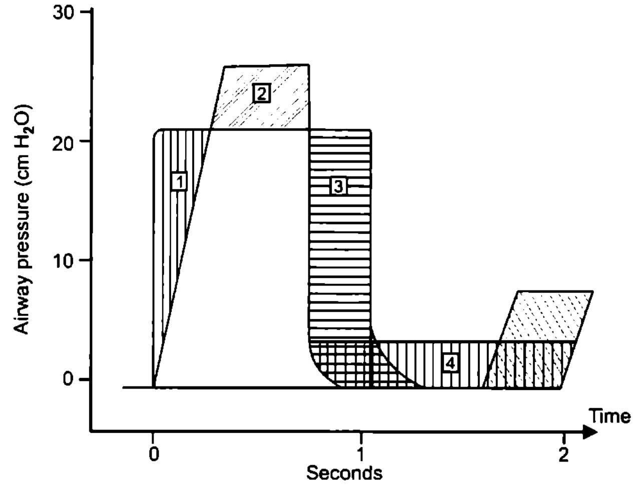


Fig. 33.4: Factors affecting mean airway pressure and oxygention (1) and (3) inspiratory time, (2) peak inspiratory pressure, and (4) positive and expiratory pressure (PEEP)

5. Do not forget other measures to improve oxygenation
   a. Normalize cardiac out put (if low output) by fluids and/inotropes
   b. Maintain normal hemoglobin
   c. Maintain normothermia
   d. Deepen sedation/consider neuromuscular block.

High $PaCO_2$

Common reasons include hypoventilation, dead-space ventilation (too high PEEP, decreased cardiac output, pulmonary vasoconstriction), increased CO_2 production, hyperthermia, high carbohydrate diet, shivering.

Inadequate tidal volume delivery (hypoventilation) will occur with endotracheal tube block, malposition, kink, circuit leak, ventilator malfunction.

Measures for High $PaCO_2$

Guidelines

1. If volume limited: Increase tidal volume (Vt), Increase frequency (rate) (F)
   If asthma :Increase expiratory time,may need to decrease rate to achieve an I:E ratio > 1:3.
2. If pressure limited: Increase peak inspiratory pressure (PIP), decrease PEEP, increase frequency (rate)
3. Decrease dead space(increase cardiac output, decrease PEEP, vasodilator)
4. Decrease CO_2 production: Cool, increase sedation, decrease carbohydrate load
5. Change endotracheal tube if blocked, kinked, malplaced or out, check proper placement
6. Fix leaks in the circuit, endotracheal tube cuff, humidifier

Measures to Reduce Barotrauma and Volutrauma

Following concepts are being increasingly followed in most pediatric intensive care units.

1. **Permissive Hypercapnia**[9]: Higher $PaCO_2$ are acceptable in exchange for limiting peak airway pressures:as long as pH>7.2
2. **Permissive Hypoxemia:** PaO_2 of 55-65; SaO_2 88-90 percent is acceptable in exchange for limiting FiO_2 (<.60) and PEEP, as long as there is no metabolic acidosis.

Adequate oxygen content can be maintained by keeping hematocrit > 30 percent.

Patient ventilator dysynchrony: Incoordination between the patient and the ventilator: Patient fights the ventilator.

Common causes include, Hypoventilation, hypoxemia, tube block/kink/malposition, bronchospasm, pneumothorax, silent aspiration, increased oxygen demand/increased CO_2 production (in sepsis), inadequate sedation.

If patient fighting the ventilator and desaturating: Immediate measures.

Use pneumonic: DOPE, D displacement, O obstruction, P pneumothorax, E equipment failure

1. Check tube placement.When in doubt take the endotracheal tube out, start manual ventilation with 100 percent oxygen
2. Examine the patient: Is the chest rising? Breath sounds present and equal? Changes in exam? Atelectasis, treat bronchospasm/tube block/malposition/pneumothorax? (Consider needle thoracentesis)
   Examine circulation: Shock? Sepsis?
3. Check arterial blood gas and chest X-ray for worsening lung condition, and for confirming pneumothorax.
4. Examine the ventilator, ventilator circuit/humidifier/gas source.

If no other reason for hypoxemia: Increase sedation/muscle relaxation, put back on ventilator.

Sedation and Muscle Relaxation during Ventilation

Most patients can be managed by titration of sedation without muscle relaxation (See Chapter on Sedation). Midazolam (0.1-0.2 mg/kg/hr) and vecuronium drip (0.1-0.2 mg/kg/hr) is most commonly used. Morphine or fentanyl drip can also be used if painful procedures are anticipated.

Routine Ventilator Management Protocol

Following protocol is commonly followed

1. Wean FiO_2 for SpO_2 above 93-94
2. ABG one hour after intubation,then am pm schedule (12 hourly), every AM ABG in stable patients, after major ventilator settings change, and 20 min after extubation.

3. Pulse oximetry on all patients, End tidal carbondioxide ($EtCO_2$)/graphics monitoring if available
4. Frequent clinical examination for respiratory rate, breath sounds, retractions, color
5. Chest X-ray every day/alternate day/as needed.

Respiratory Care Protocol (See Chapter on Respiratory Care)

1. Position change 2 hourly right chest tilt/left chest tilt/supine position.
2. Suction 4 hourly and as needed(In line suction to avoid de recruitement/loss of PEEP/desaturation if available)
3. Physiotherapy 8 hourly. Percussion, vibration and postural drainage. NO physiotherapy if labile oxygenation such as ARDS (Acute respiratory distress syndrome), PPHN (persistent pulmonary hypertension of neonate)
4. *Nebulization:* In line nebulization is preferred over manual bagging. Metered dose inhalers (MDIs) can also be used.
5. Disposable circuit change if visible soiling.
6. Humidification/in line disposable humidifier.

Disease Specific Ventilation

Status asthmaticus[10,11]

Main Indications are clinical deterioration despite maximal drug therapy.
Rising $PaCO_2$ (40 to 45 mm) from a low $PaCO_2$ (25 to 30 mm)
Fatigue, lethargy, deteriorating mental status
Mixed respiratory and Metabolic acidosis

Initiation of Ventilation

- Controlled intubation use sedation and muscle relaxation (short acting muscle relaxant such as succinyl choline.
- Use cuffed endotracheal tube if feasible
- Ketamine with midazolam are good sedatives for initiation and maintenance of mechanical ventilation
- Mechanical Ventilation in asthma is associated with high morbidity and mortality
- Risks involved include barotrauma (air leak) due to dynamic hyperinflation, impaired venous return (tamponade) and Low cardiac output due to hyperinflation (pulsus paradoxus). Strategies that minimize end expiratory volume, intrinsic auto peep, and maximize expiratory time, using lower tidal volumes and respiratory rates with permissive hypercapnia have been shown to be associated with lower mortality.

Ventilation Strategies

Controlled Hypoventilation using SIMV or Assist Control

Volume or pressure limited mode

Plateau pressure limit must be < 35 cm water

Tidal volume 6-10 ml/kg for 8-14/min, PEEP 3-4 cm H_2O

Support Modes: Volume or Pressure Support

Patient determines (f) rate and (Ti) inspiratory time
Plateau pressure limit set at < 35 cm water
Tidal vol 6-10 ml/kg

Patient can determine the respiratory cycle, frequency and flow pattern, there is active exhalation and decreased end expiratory lung volume.
As plateau pressure falls, barotrauma decreases

Use of PEEP

In conscious patient not on muscle relaxants,on assist control mode, PEEP can be used in physiological levels (3-4 cm H_2O). Application of extrinsic PEEP (at levels less than intrinsic or auto PEEP) helps decrease work of breathing and easier patient triggering. In some ventilators level of auto PEEP can be monitored.

Controlled Hypercapnia[9]

Both pressure control or volume control can be used as long as plateau pressures do not exceed,[35] rates are et 8 to 14 (I:E ratio 1:3 or more), use of prolonged expiration to avoid intrinsic PEEP and delivered tidal volume 6 to 10 ml/kg. In volume control mode PIP may go too high. Advantage of Pressure control mode is that decelerating flow delivers volume at a lower inspiratory pressure. Strategies of permissive hypercapnea and permissive hypoxemia are generally acceptable to minimize barotrauma and airleak.

CASE SCENARIO 1

A 10 year old boy weighing 25 kg comes to the emergency with history of fever and cough for 2 days and has developed respiratory distress for past 3 hours. He is a known case of Bronchial Asthma on regular Fluticasone inhaler but has stopped his inhalers for the past 10 days.

On examination, he is drowsy and lethargic. His heart rate is 130/min, respiratory rate is 40/min with severe intercostal and subcostal retractions with nasal flare. His BP is 100/74 mmHg, peripheral pulses are feeble and CFT is 4 secs. He is dusky and saturating 84 percent in air which increases to 92 percent in 100 percent Oxygen. On auscultation, he has bilateral poor air entry and a chest X-ray done of him reveals bilaterally hyperinflated lung fields. He was immediately intubated and ventilated for impending respiratory failure. He was initiated on PRVC mode of ventilation with the following settings.

1 Tidal volume 150 ml (6 ml/kg)
2 FiO_2 100 percent
3 Rate 12
4 I:E ratio 1:3
5 PEEP 3

His ABG on the above settings was:

pH 7.15, PCO_2 90, PO_2 96, HCO_3 20.1, sat 99 percent and BE –6

Following this rate was decreased to 8 and FiO_2 to 80 percent such that his I:E ratio increased to 1:4. The repeat ABG revealed a pH of 7.26, pCO_2 72, pO_2 76, HCO_3 23, saturation 96 percent and BE –2. He was continued on the same settings allowing for some permissive hypercapnia as discussed earlier.

Ventilation for Acute Respiratory Distress Syndrome (ARDS)

Indications for ventilation in ARDS are essentially based on clinical evidence of hypoxemia, and include:

1. Increasing respiratory distress
2. Tachypnea,tachycardia, accessory muscle use (In late stage apnea/bradycardia)
3. Increasing oxygen requirement with desaturation on maximal oxygen
4. Respiratory fatigue/lethargy
5. To reduce work of breathing

Goals of Ventilation in ARDS

Ventilation should be delivered with minir volutrauma to lungs(using low tidal volumes :6-8r kg),[12] minimal tolerable inspired oxygen with PI (positive end expiratory pressure) to achieve Pa 55 to 80mm Hg and maximal tolerable arterial PC (50 to 60 mm Hg) with arterial pH > 7.25 (permiss hypercapnia),[13] and absence of metabolic (hypo: acidosis. Conventional ventilation is the most reac available modality. Earlier standard approach u: to be:Volume ventilation with tidal volumes 1C 15 ml/kg with positive end expiratory pressı Adequate filling pressures with use of fluid and gc cardiac contractility with inotropic support prevent low cardiac output.

Problems with conventional 10 to 15 ml/kg ti volume and PEEP are as follows:

Barotrauma, volutrauma, air leak (pneumothora chronic lung disease, delayed recovery, poor carc out put, prolonged ventilation and nosocom infections.

In view of problems with conventional ti volume ventilation: Low tidal volume strategy recommended (NIH ARDS Network study).[12]

This was a prospective randomized multicer trial of 240 patients with two groups using 12 ml, vs 6 ml/kg tidal volume, PEEP 5 to 18 cm of H FiO_2 0.3 to 1, showed 25 percent reduction mortality in 6 ml/kg group. In another study, use higher positive end expiratory pressure with lov tidal volumes (Open lung approach)[13,14] has be used with improved results. Gattinoni et al in adı and Marraro in pediatrics ARDS patients, show that chest CT (computerised tomography) may useful to see the extent of pulmonary involveme Gattinoni studied benefits of prone positioning[1 patients with ARDS with underventilated poste zones.Prone positioning is being recommenc although transient improvement in oxygenat occurs but no real effect on improving long te outcomes has been shown. Problems associated w prone positioning include difficulty in nurs management and monitoring (chances of accider extubation, especially during X-ray examination, a physiotherapy). At authors institution, use of l tidal volume strategy was studied with retrospective controls where 10-15 ml/kg tidal volume was used in children with ARDS showing improvement in oxygenation but no difference in outcomes.[16]

Currently no good pediatric studies are available on use of prone positioning in ARDS patients and the effect on outcomes.

CASE SCENARIO 2

A 5 year old, premorbidly well child weighing 15 kg comes to emergency with 3 days of moderate to high grade fever and cough. He has been lethargic for the past 1 day and is not feeding well. Mother noticed that he is breathing fast since morning and has become dusky and unresponsive for the past 10 mins. On examination, he is unresponsive with a heart rate of 140/min, respiratory rate 60/min with retractions and head bobbing. He is peripherally cyanosed, saturating 80 percent in air and saturations slowly increasing to 88 percent in 100 percent Oxygen. Auscultation reveals bilateral extensive crepitations. The chest X-ray is suggestive of ARDS with bilateral diffuse infiltrates in lungs.

He was intubated and ventilated on PRVC mode. His initial settings were:

1. Tidal volume 90 ml (6 ml/kg)
2. FiO_2 100 percent
3. Rate 25
4. I:E ratio 1:2
5. PEEP 6

His saturations improved to 85 percent on the above settings and an ABG done showed pH 7.30, pCO_2 45, pO_2 47, HCO_3 20.4, BE –5 and saturation 85 percent. To improve his oxygenation, his PEEP was increased to 8 and I:E ratio to 1:1. Following the intervention, his saturations improved to 95 percent.

Airleak Syndrome

Pneumothorax, Bronchopleural Fistula

Ventilation for airleak syndrome is challenging.Chest tubes are frequently required

Ventilation Strategies

Using low mean airway pressures, low Peak inspiratory pressures, low PEEP, lower tidal volumes, and lower inspiratory times are needed.

Other Modes useful in Airleak Syndrome

- High Frequency Oscillatory Ventilator (HFOV) delivers small tidal volumes at high frequency with lower peak and mean airway pressures.
- Patient has to be muscle relaxed.
- Patient cannot be suctioned frequently as disconnecting the patient from the oscillator can result in volume loss in the lung.
- Likewise, patient cannot be turned frequently so decubitus ulcers can occur.
- Patient should be turned and suctioned 1-2 times/day if he/she can tolerate it.

Postoperative Ventilation following Open Heart Surgery

General Principles

One needs to understand the cardiac physiology associated with the lesion and corrective surgery as well as cardiopulmonary interactions in the postoperative period.

Hypoxia and hypercarbia should be avoided to prevent pulmonary hypertension that increases right ventricular afterload/chances of Right ventricular failure.

Excessive systemic vasoconstriction should be avoided to prevent increase in LV afterload.

Volume/pressure limited ventilation: Mode of ventilation has not shown to make any real difference in outcomes.

Excessive PEEP and excessive mean airway pressures should be avoided to prevent tamponade/low cardiac output.

Pulmonary and systemic vascular resistance can increase with pain causing increased after load on the heart.

Consider nitric oxide in patients with severe preoperative pulmonary hypertension,in post operative period.

Chronic lung disease/Neuromuscular weakness: Tracheostomy is usually performed.

One needs to assess need for Day/Night/ home ventilation.

Generally low ventilator settings are needed. LP60 (USA) pressure controlled ventilator can be used.

Non-invasive positive pressure ventilation can also be tried to deliver PS and CPAP via tight fitting mask (BiPAP: Bi-level positive airway pressure). One can set a "back up" rate in case of apnea.

CASE SCENARIO 3

A 13 year old immunized female child weighing 30 kg was admitted with complaints of sudden onset weakness of lower limbs with inability to stand and bear weight for 2 days. The next day she developed weakness of both upper limbs such that she could only move her arms in the bed. She started to have decreased volume of voice and complained of some tingling sensation in both legs. There was no history of fever, cough, loose stools, trauma, alteration in sensorium or seizures. She had an episode of fever with cough 2 weeks back which lasted for 3-4 days. On examination she was alert, conscious and oriented. Her heart rate was 110/min and respiratory rate 30/ min. She had shallow respiratory efforts with paradoxical respiration. CNS examination revealed quadriparesis with power in both lower limbs and upper limbs being 1/5 and 2/5 respectively. She had global areflexia. There was no objective sensory loss and no other focal deficits. She was diagnosed to have Gullian-Barre syndrome with respiratory muscle weakness supported by NCV findings. She was ventilated for neurogenic cause of respiratory failure on PRVC mode of ventilation with the following settings:

Tidal volume 200 (6-7 ml/ kg)
Rate 15
FiO_2 40%
Peep 3
I : E ratio 1: 2

His ABG on the above settings was within normal limits.

Raised ICP (Intracranial Pressure)

Following points should be kept in mind.

1. Avoid ketamine, succinyl choline as these agents raise ICP.
2. Midline head up position is ideal.
3. Adequate sedation and muscle relaxation is required to prevent coughing and bucking on the ventilator(leads to raised ICP) and adequate analgesia during painful procedures.
4. Low PEEP (avoidance of excessive PEEP) to prevent ICP from going up.
5. Goal of ventilation to keep normal PaO_2 and $PaCO_2$ 30-35 mm Hg; hyperventilation is no longer recommended.[17]

Neonatal Ventilation[18]

Continuous positive airway pressure (CPAP)[19]: A continuous flow of heated humidified gas is circulated past the infants airway at a set pressure of 3-8 cm of H_2O maintaining an elevated end expiratory lung volume while the infant breathes spontaneously.CPAP is usually delievered by means of nasal prongs or nasopharyngeal tube. It improves oxygenation by an increase in the functional residual capacity. However, over reliance on CPAP may be dangerous and it should only be used if infants show adequate respiratory effort, appear to be tolerating the procedure well and maintain adequate arterial blood ($PCO_2 < 50$ mmHg, pH > 7.25, $PaO_2 > 50$).

With all CPAP devices some air may get into the gut and cause gastric distension. This can be prevented by using an open ended orogastric tube-in-situ. CPAP effectively splints the chest wall, keeps the airways patent thereby preventing obstructive apnoeas and atelectasis.various studies have documented the efficacy of CPAP in respiratory distress(Hyaline membrane disease) of mild to moderate degree.[19] Recently trials have been conducted on using nasal intermittent positive pressure (NIPPV) and it has been found to have similar results as CPAP.

Conventional Neonatal Ventilation[20,21]

Pressure Limited Time Cycled Ventilation

The commonest type of ventilation used for neonates is pressure limited, time cycled ventilation where a peak inspiratory pressure is set and gas is delivered to achieve that target pressure. After the target is reached, the remainder of the gas volume is released into the atmosphere as a result the tidal volume delivery with each breath is variable despite the recoeded peak pressure being constant. Inspiration also ends after a preset time period.

In contrast, in volume limited modes, a preset volume is delivered with each breath regardless of the pressure that is needed. Some ventilators also use airway flow as the basis of cycling in which inspiration ends when flow has reached a critical low or preset level (flow-cycled ventilation).

In pressure limited, time cycled continuous flow ventilators following parameters are set at the outset:

Peak inspiratory pressure (PIP)
Peak end expiratory pressure (PEEP)
Inspiratory time (ti)
Rate

This system is relatively simple and maintains good control over respiratory pressures.

Disadvantages

- Poorly controlled tidal volume.
- Does not respond to changes in respiratory compliance.
- Spontaneously breathing infants may receive inadequate ventilation and are at increased risk for airleaks.

CASE SCENARIO 4

A neonate is born to a 24 year old primigravida with pregnancy induced hypertension(PIH) through lower segment cessarian section due to uncontrolled hypertension at 34 weeks of gestation. He had a birth weight of 1.8 kg. He was tachypneic at birth with a rate of 68/min and subcostal, intercostal and sternal retractions. He had grunting and had pulse oximeter saturations at 85 percent in roomair which picked to 94 percent in oxygen. The chest X-ray revealed bilateral homogenous opacities suggestive of hyaline membrane disease (HMD). He was intubated and ventilated on pressure limited time cycled mode of ventilation with the following settings:

PIP 22
PEEP 4
FiO_2 100%
Rate 50
Inspiratory time 0.4 sec

His ABG on the above settings showed a pH of 7.25, pCO_2 60, pO_2 68, HCO_3 18, BE –5.0 and sats 95 percent. His ventilatory settings were revised to a PIP of 24 and rate was increased to 55. Following this his pCO_2 came down to 44 and pH normalized.

Alternative Modes of Neonatal Ventilation

Due to disadvantages associated with conventional ventilation, following alternative strategies are being used increasingly.

Patient triggered ventilation (PTV): This is a form of ventilation where machine delivered breath is initiated in response to a signal derived from the patient's own inspiratory effort thus synchronizing the onset of both spontaneous and mechanical breaths. The types of signals used to provide PTV to newborn vary and could be impedence, pressure or flow. The basic feature is shifting of control of breathing from clinician to patient and the newer generation of ventilators allow its application to the smallest of babies. PTV can be of following types.

(a) **Assist/control ventilation:** This is the best mode of ventilation in acute phase of illness as it requires least amount of patient effort and produces improved oxygenation at the same or lower mean airway pressure than conventional modes. In this type of ventilation a positive pressure breath is delivered in response to patient's inspiratory effort (assist) provided it exceeds a preset threshold criteria. There is a back-up rate (control) in case patient stops breathing. The inspiratory flow is proportional to patient effort and ventilation is tolerated well.

(b) **Synchronous intermittent mandatory ventilation (SIMV):** In this mode of ventilation mechanically delivered breaths are cycled at a rate set by the clinician but are synchronized to the onset of the patient's own breath.Patient breathes freely inbetween the mechanical breaths. This insures less risk of 'fighting' or airleaks and sedation is not required. SIMV is particularly helpful for weaning from ventilation.[21]

(c) **Pressure support ventilation(PSV):** This is similar to assist/control ventilation except that it is flow cycled, thus patient has full control over how much to breathe and for how long(ti). Although PSV can be used for full ventilation(PSV max), in practice it is genarally used as a weaning mode.

(d) **Proportional assist ventilation (PAV).**

(e) **Mandatory minute ventilation (MMV):** These are other promosing ventilatory strategies currently under development for clinical use but no data is available relating to its use in neonates.

Rescue Strategies for Management of Neonatal Ventilatory Failure

Despite improved ventilatory techniques, conventional ventilation may fail in certain situations. A commonly used parameter to assess the efficacy of ventilation is **oxygenation index** (OI).

$$OI = \frac{P_{AW} \times FiO_2 \times 100}{PaO_2}$$

P_{AW} = Mean airway pressure
FiO_2 = Concentration of inspired oxygen
PaO_2 = Partial pressure of oxygen
OI of 25-40 indicates insufficient ventilation with existing mode of support.
OI of > 40 indicates respiratory failure.
Various rescue therapies as given below are currently practiced.

(A) *High Frequency Ventilation:* This can be of two types
High Frequency Oscillatory Ventilation (HFOV)
High Frequency Jet Ventilation (HFJV)

In newborns high frequency oscillation has been found to be effective in certain situations. During this type of ventilation a continuous flow of fresh gas rushes past the source that generates the oscillation and a controlled leak or low pass filter allows the gas to exit the system. Both inspiration and expiration are active processes. Oscillations are generated at a frequency ranging from 3 HZ-15 HZ (1 hurst (HZ) = 60 breaths) per minute. Pressure oscillations within the airway produce tiny tidal volume fluctuations around a constant distending pressure. The amplitude of the pressure, which varies from 15-50 cm H_2O, determines the tidal volume. This ventilation causes uniform recruitment of alveoli and there is significantly lower risk of airleaks. Earlier studies on HFOV had raised some doubts about the risk of IVH however randomized controlled trials carried out with proper selection criteria have depicted a significantly better outcome with HFOV in certain conditions.[22] This mode of ventilation has been found to be effective in respiratory distress complicated by PPHN.[23] Only Sensorimedics 3100/3100A, a high frequency oscillator has been approved by FDA for early intervention (prophylactic HFOV) but it is not commonly preferred form of therapy.

CASE SCENARIO 5

A 29 year old 2nd gravida mother delivered at 38 weeks of gestation by lower segment cessarian section in view of Meconium stained liquor (MSL). At birth the baby was crying vigorously. He developed respiratory distress soon after birth. He was breathing at a rate of 80/min with severe retractions and was saturating 88 percent in 100 percent oxygen. His chest X-ray was suggestive of meconium aspiration syndrome (MAS). He was ventilated due to persistent hypoxia on the following settings:

Mode : Pressure limited time cycled
PIP 26
PEEP 3
Rate 60
FiO_2 100%
I:E ratio 1:3

His post ventilation ABG was : pH 7.182, pCO_2 56, pO_2 40, HCO_3 16.2, BE – 7.5 and oxyhemoglobin sauration at 86 percent. An echocardiogram was done on suspicion of persistent pulmonary hypertension (PPHN) which showed pulmonary pressures of 90 mm Hg with systemic pressure being 82/40. He was started on dopamine to increase the systemic pressure and Milrinone for pulmonary vasodilation. Sodium bicarbonate was given to correct acidosis and PIP was increased to 28. I:E ratio was not increased due to a high risk of air leaks in MAS. After these interventions the ABG improved to pH 7.24, pCO_2 45, HCO_3 19.6, BE – 2.6 but pO_2 remained low on 45 mm Hg. He was given a trial of high frequency ventilation on which his hypoxia slowly improved.

High Frequency Jet Ventilation is a variant of HFOV and the differences are tabulated below

	HFJV	HFOV
Rate(HZ)	1.5-3.00	3.00-15
Expiration	PASSIVE	ACTIVE
Special ETT (reintubation)	YES	NO
Gas Exchange	++	++
$PaCO_2$ reduction	++	++
PaO_2 increase	+-	+
Cardiac output	+-	_
Tracheal injury	++	?

Inhaled Nitric Oxide (INO)

Nitric oxide (NO) appears to be ubiquitously distributed within universe. Critical care physicians have been most interested in the profound regulatory effects of NO on vascular tone. Inhaled nitric oxide distributes only to aerated lung where it rapidly diffuses from endothelial cells into subjacent vascular smooth muscle cells and stimulates Guanylate Cyclase to increase the concentration of Cyclic Guanosine Monophosphate that in turn causes smooth muscle relaxation. This localized vasodilator effect improves V/Q mismatch. NO that diffuses into vascular space is quickly converted to methaemoglobin thereby avoiding systemic vasodilator effect. Inhaled nitric oxide is particularly useful for treating persistent pulmonary hypertension complicating RDS. This can be used with both conventional and high frequency ventilation. Kinsella et al have reported outcome in nine cases of PPHN treated with INO. Within 15 minutes of initiation, PaO_2 increased from 55 mmhg to 136 mmhg and OI reduced from 60 to 26.[24] The first three had to be shifted to ECMO but the remaining six recovered completely.

Patients with pulmonary hypertension secondary to congenital heart disease may also benefit both diagnostically and therapeutically from NO. Sometimes NO may combine with O_2 to form NO_2 and peroxynitrite, which could be highly toxic to the body. Thus further studies are required to confirm the short term and long term safety of INO usage in very young infants. The dose range used (10-80 parts per million) also needs to be standardized.

Summary

1. Remember shock and post resuscitation are important indications for ventilation, in addition to respiratory failure and neuromuscular disease.
2. Clinical monitoring of adequate chest rise and oxygen saturations is very important (regardless of volume,pressure or time cycled mode).
3. If ventilator fails, or when in doubt,remove endotracheal tube and try bag mask ventilation.
4. Think about pneumothorax in a patient on mechanical ventilation
5. Pulse oximetry and ABG facility is necessary for ventilation
6. Hypoxia should be ruled out/corrected before sedating an agitated child.
7. Do not muscle relax/sedate patient with upper airway obstruction unless very confident in endotracheal intubation.
8. Low tidal volume is permitted to prevent lung trauma(permissive hypercapnia)
9. Endtidal CO_2 monitoring and pulmonary graphics monitoring is desirable if available.

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CHAPTER

34

Structure and Function of a Conventional Ventilator

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This chapter is intended to get the reader familiar with basic aspects of the ventilator as a machine and its functioning. We feel this has important bearing in the management issues of a critically ill child requiring mechanical ventilation.

Ventilator

A ventilator is an automatic mechanical device designed to move gas into and out of the lungs. The act of moving the air into and out of the lungs is called breathing, or more formally, ventilation.

Simply, compressed air and oxygen from the wall is introduced into a ventilator with a blender, which can deliver a set FiO_2. This air oxygen mixture is then humidified and warmed in a humidifier and delivered to the infant by the ventilator via the breathing circuit.

The peak inspiratory pressure (PIP) or tidal volume (Vt), positive end expiratory pressure (PEEP), inspiratory time and respiratory rate are set on the ventilator.

The closing of the exhalation valve initiates a positive pressure mechanical breath. At the end of the preset inspiratory time, the exhalation valve is opened, permitting the infant to exhale. If this end is partly occluded during expiration a PEEP is generated in the circuit proximal to the occlusion (or CPAP if the infant is breathing spontaneously). Expiration is passive and gas continues to flow delivering the set PEEP.

Parts of a Ventilator

1. *Compressor:* This is required to provide a source of compressed air. An in-built wall source of compressed air, if available, can be used instead. It draws air from the atmosphere and delivers it under pressure (50 PSI) so that the positive pressure breaths can be generated.

   The compressor has a filter which should be washed with tap water daily or as directed. If this is not done, it greatly increases the load on the compressor. The indicator on the compressor should always be in the green zone. It should not be placed too close to the wall as it may get overheated. There should be enough space to permit air circulation around it.
2. *Control panel:* The controls that are found on most pressure-controlled ventilators include the following:
   - FiO_2
   - Peak Inspiratory Pressure: PIP (in pressure controlled ventilators).
   - Tidal volume/Minute volume (in volume controlled ventilators).
   - Positive End Expiratory Pressure (PEEP).
   - Respiratory Rate (RR).
   - Inspiratory Time (Ti).
   - Flow rate.

The other parameters displayed on the ventilator include mean airway pressure (MAP), I:E ratio (ratio of the inspiratory time to expiratory time). The expired tidal volume will be displayed in all volume controlled ventilators and some pressure controlled ventilators.

Newer ventilator models have digital display controls some ventilators also display waveforms, which show the pulmonary function graphically.

3. *Humidifier:* Since the endotracheal tube bypasses the normal humidifying, filtering and warming system of the upper airway the inspired gases must be warmed and humidified to prevent hypothermia, inspissation of secretions and necrosis of the airway mucosa.

   Types of humidifiers available:

   1. *Simple humidifier:* It heats the humidity inspired gas to a set temperature, without a servo control. The disadvantage is excessive condensation in the tubings with reduction in the humidity along with cooling of the gases by the time they reach the patient.
   2. *Servo-controlled humidifier with heated wire in the tubings:* These prevent accumulation of condensate while ensuring adequate humidification. Optimal temperature of the gases should be 36-37°C and a relative humidity of 70 percent at 37°C. If the baby is nursed in the incubator temperature, monitoring must take place before the gas enters the heated field. At least some condensation must exist in the inspiratory limb which shows that humidification is adequate. The humidifier chamber must be changed daily. It should be adequately sterilized or disposable chambers may be used.
4. *Breathing circuit:* It is preferable to use disposable circuits for every patient. Special pediatric circuits are available in the market with water traps. If reusable circuits are used they must be changed every 3 days. Reusable circuits are sterilized by gas sterilization or by immersion in 2 percent glutaraldehyde for 6-8 hours and then thoroughly rinsing with sterile water. Disposable circuits may be changed every week.

Terminology

Ventilatory controls that can be altered in mechanical ventilation include the following:

1. Inspired oxygen concentration (FiO$_2$)
2. Peak inspiratory pressure (PIP)
3. Flow rate
4. Positive end-expiratory pressure (PEEP)
5. Respiratory rate (RR),or Frequency (f)
6. Inspiratory/Expiratory Ratio (IE Ratio)
7. Tidal volume (in volume controlled ventilators)
8. Pressure support.

Inspired Oxygen Concentration (FiO$_2$)

An improvement in oxygenation may be accom lished either by increasing the inspired oxyg concentration (FiO$_2$) or by different ventilat settings.

1. Increasing peak inspiratory pressure (PIP)
2. Increasing inspiratory/expiratory ratio
3. Applying a positive pressure before the end expiration (PEEP).

FiO$_2$ is adjusted to maintain an adequate Pa High concentrations of oxygen can produce lu injury and should be avoided. The exact thresho of inspired oxygen that increases the risk of lu injury is not clear. A FiO$_2$ of 0.5 is generally con dered safe. In patients with parenchymal lung disea with significant intrapulmonary shunting, the maj determinant of oxygenation is lung volume which a function of the mean airway pressure. With a shu fraction of >20 percent (see Chapter on Equations the PICU) oxygenation may not be substantial improved by higher concentrations of oxygen.

The administration of oxygen and its toxicity is clinical problem in the treatment of neonates, espe ally low birth weight infants.

The developing retina of the eye is highly sen tive of any disturbance in its oxygen supply. Oxyg is certainly a critical factor (hyperoxia, hypoxia), b a number of other factors (immaturity, blo transfusions, PDA, vitamin E deficiency, infection may interact to produce various degrees Retinopathy of Prematurity (ROP).

Another complication of oxygen toxicity induce by artificial ventilation in the neonatal period is chronic pulmonary disease, Bronchopulmona Dysplasia (BPD), mostly seen in premature infan ventilated over long periods with a high inspirato peak pressure and high oxygen concentration.

High oxygen concentration may play a role the pathogenesis of BPD (bronchopulmona dysplasia), but recent studies have shown, that t severity of the disease is correlated to the Pe inspiratory pressure (PIP) during artificial Ventilati rather than to the doses of supplementary oxyge

Peak Inspiratory Pressure (PIP)

Peak Inspiratory Pressure in the major factor in dete mining tidal volume in infants treated with ti cycled or pressure cycled ventilators. Most ventilators indicate inspiratory pressure on the front and it can be selected directly.

The starting level of PIP must be considered carefully. Critical factors that must be evaluated are the infants weight gestational age (the degree of maturity), the type and severity of the disease and lung mechanics—such as lung compliance and airway resistance.

The lowest PIP necessary to ventilate the patient adequately is optimal. In most cases, associated with increased tidal volume, increased CO_2 elimination and decreased $PaCO_2$.

Mean airway pressure will rise and thus improve oxygenation.

If PIP is minimized there is a decreased incidence of barotrauma with resultant air leak (pneumothorax and pneumomediastinum) and BPD.

Hacker *et al* demonstrated that more rapid ventilator rates and lower PIP are associated with a decreased incidence of air leaks—a mode of ventilation which may be recommended in infants with congenital diaphragmatic hernia.

High PIP may also impede venous return and lower cardiac output.

Flow Rate

The flow rate is important determinant during the infant's mechanical ventilation of attaining desired levels of peak inspiratory pressure, wave form, I:E ratio and in some cases respiratory rate.

In general, a minimum flow at least two times the minute volume ventilation is usually required. Most pressure ventilators operate at flows of 6-10 liters per minute.

If low flow rates are used, there will be a slower inspiratory time (Ti) resulting in a pressure curve of sine wave form and lowering the risk of barotrauma.

Too low flow relative to minute volume may result in hypercapnia and accumulation of carbon dioxide in the system.

High inspiratory flow rates are needed if square wave forms are desired and also when the inspiratory time is shortened in order to maintain an adequate tidal volume. Carbon dioxide retention in the ventilator tubing will be prevented at high flow rates.

A serious side effect of high flow rate is an increased risk of alveolar rupture, because maldistribution of ventilation results in a rapid pressure increase in the non-obstructed or non-atelectatic alveoli.

Positive End Expiratory Pressure (PEEP)

Positive pressure applied at the end of expiration to prevent a fall in pressure to zero is called Positive End Expiratory Pressure (PEEP).

PEEP stabilizes alveoli, recruits lung volume and improves the lung compliance. The level of PEEP depends on the clinical circumstances. Application of PEEP results in a higher mean airway pressure, and mean lung volumes.

The goals of PEEP are:

1. increasing FRC above closing volume to prevent alveolar collapse,
2. maintaining stability of alveolar segments,
3. improvement in oxygenation, and
4. reduction in work of breathing.

The optimum PEEP is the level at which there is an acceptable balance between the desired goals and undesired adverse effects. The desired goals are: (1) reduction in inspired oxygen concentration—nontoxic levels (usually less than 50%); (2) maintenance of PaO_2 or SaO_2 of > 60 mm Hg or > 90 percent respectively (3) improving lung compliance; and (4) maximizing oxygen delivery.

Arbitrary limits cannot be placed to determine the level of PEEP or mean airway pressure that will be required to maintain adequate gas exchange. When the level of PEEP is high, peak inspiratory pressure may be limited to prevent it from reaching dangerous levels that contribute to air leaks and barotrauma. In children with tracheomalacia or bronchomalacia, PEEP decreases the airway resistance by distending the airways and preventing dynamic compression during expiration.

The compliance may be improved. Improved ventilation may result (improvement in ventilation/perfusion ratio) by preventing alveolar collapse.

Low levels of PEEP (2-3 cm H_2O) are often used during weaning from the ventilator in conjunction with low IMV rates only for a short amount of time.

Medium levels of PEEP (4-7 cm H_2O) are commonly used in moderately ill patients.

High levels of PEEP (8-10 cm H_2O) benefit oxygenation in ARDS (Acute Respiratory Distress Syndrome); tidal volume, and PaO_2 increases.

Higher PEEP level can also reduce blood pressure and cardiac output increased explained by a reduced preload. Very high levels of PEEP results in over distention and alveolar rupture leading to increased incidence of pneumothorax and pneumomediastinum.

Respiratory Rate (RR) or Frequency (f)

Respiratory rate, together with tidal volume, determines the minute ventilation. Depending on the infant's gestational age and the underlying disease, the resulting pulmonary mechanics (resistance, compliance) require the use of slow or rapid ventilatory rates.

Moderately high ventilator rates (60-80 breaths per minute) employ a lower tidal volume and therefore lower inspiratory pressures (PIP) are used to prevent barotrauma.

High rates may also be required to hyperventilate infants with pulmonary hypertension and right-to left shunting to achieve an increased pH and reduced $PaCO_2$ thereby reducing pulmonary arterial resistance and shunting associated with increased $PaCO_2$. Respiratory rate is the primary determinant of minute ventilation and hence CO_2 removal from lungs.

Tidal volume × RR, increasing the RR lowers the $PaCO_2$ level. A respiratory rate of 40-60 is usually sufficient in most conditions. High rates are necessary in Meconium Aspiration Syndrome (MAS) where CO_2 retention is a major problem. It must be recognised that increasing the RR while keeping the IT the same shortens expiration and may lead to inadequate emptying of lungs and inadvertent PEEP.

One of the major disadvantages in using the high ventilator rates is an insufficient emptying time during the expiratory phase, resulting in air trapping, increased functional residual capacity (FRC), and thus decreased lung compliance.

A slow ventilation the rate combined with a long inspiratory time both in animals and infants with RDS resulted in fewer bronchiolar histological lesions better lung compliance and in infants, a reduction in the incidence of BPD.

Ratio of Inspiratory to Expiratory Time (I:E ratio)

One of the most important ventilator control is the ratio of inspiratory to expiratory time (I:E ratio). This ventilator control has to be adjusted depending on the pathophysiology and the course of the respiratory disease, always with respect to pulmonary mechanics, such as compliance, resistance and time constant.

In infants with, Respiratory, distress Syndrome with decreased compliance but normal resistance, resulting in shortened time constants inspiratory times I:E with ratios 1:1 are usually used.

Reversed I:E ratios, as high as 4:1 have been shown to result in improvement in oxygenation and in a retrospective study decreased the incidence of BPD. Other investigators also advocated the use of prolonged inspiratory time, since infants in the '2:1' group required less inspired oxygen and a lower expiratory pressure to achieve satisfactory oxygenation. Extreme reversed I:E ratio with a short expiratory time will lead to air trapping and alveolar distension. In addition, prolonged inspiratory time may adversely affect venous return to the heart and decrease pulmonary and systemic blood flow. The concept becomes especially important when higher respiratory rates are used.

If inspiratory time is shorter than three to five time constants, inspiration will not be complete and tidal volume will be lower than expected. If expiratory time is too short, expiration will not be complete which will lead to air trapping.

An IT of 3-0.5 sec is sufficient for most disorders. In low compliance condition like RDS (respiratory distress syndrome) use closer to 0.5 sec. In disorders with increased airway resistance like MAS use shorter IT. Once set, IT is usually not changed unless there is persistent hypoxemia unresponsive to changes in PIP and FiO_2.

Increasing the IT shortens the expiratory time increasing the I:E ratio. Normal ratio is 1:3. Avoid 1:1 ratio to prevent air trapping.

While ventilating a case of lower airways obstruction (asthma, bronchiolitis) use short IT and slow rate as there is gas trapping and increased risk of air leaks.

Tidal Volume (Vt)

In most volume cycled ventilators tidal volume of 8 to 10 ml/kg can be set, or a particular flow rate and minute ventilation can be set to get a particular tidal volume. Siemens Servo 300 ventilator measures expired tidal volume and gives a display. If set tidal volume is higher then circuit leak or an endotracheal leak should be looked for and corrected.

Pressure-support

Pressure-support ventilation is a form of assisted ventilation where the ventilator assists a patient's spontaneous effort with a mechanical breath with a preset pressure limit. The patient's spontaneous breath creates a negative pressure, which triggers the ventilator to deliver a breath. The breath delivered is pressure-limited; very high inspiratory flow results in a sharp rise in inspiratory pressure to the preset pressure limit. The inspiratory pressure is held constant by servo-control of the delivered flow and is terminated when a minimal flow is reached (usually < 25% of peak flow), just before spontaneous exhalation begins. Pressure-support ventilation depends entirely on the patient's effort, if the patient becomes apneic, the ventilator will not provide any mechanical breath. Pressure-support ventilation allows better synchrony between the patient and the ventilator than IMV, volume-assisted ventilation, or pressure control ventilation. Pressure-support allows ventilatory muscle loads to be returned gradually during the weaning process like IMV techniques. Since each breath is assisted, it alters the pressure volume relationship of the respiratory muscles in such a way as to improve its efficiency. With ventilatory muscle fatigue, muscles can be slowly retrained and titrated more efficiently than IMV and thus promote the weaning process. The emphasis with weaning with pressure support ventilation is endurance training of the respiratory muscles, especially, the diaphragm. The parameters that can be manipulated to the titrate the muscle loading are the magnitude of the trigger threshold and the preset pressure limit. PEEP is provided to maintain FRC and prevent alveolar collapse. The amount of pressure-support to be provided depends on the clinical circumstance. A pressure-limit that delivers a VT of IO to 12 mL/kg has been termed PSV max because at this level respiratory work can be reduced to zero. It is not necessary to provide PSV max at the beginning. The level of pressure support selected should allow for spontaneous respiration without undue exertion and still result in normal minute ventilation. No strict criteria can be established; it has to be applied and titrated on an individual basis. Weaning of pressure-support ventilation is accomplished by reducing the pressure-limit decrementally. Similar to weaning guidelines previously mentioned with each wean, the effect of weaning on muscle loading has to be evaluated clinically. Increase in respiratory rate is an early indication of increasing muscle load. Retraction and use of accessory muscles would indicate a more severe muscle load. If respiratory rate increases during the weaning process, the level of pressure-support should be increased until there is reduction in the respiratory rate. While this method of weaning is attractive theoretically, its benefit in the weaning process is yet to be established in infants and children. A relative contraindication to the use of pressure-support ventilation is a high baseline spontaneous respiratory rate. There is a finite lag time involved from the initiation of a breath to the sensing of this effort and from the sensing to the delivery of a mechanical breath. In infants breathing at a relatively fast rate (40 to 50 breaths/minute), this lag time may be too long and result in asynchrony between the patient and the ventilator. Pressure-support has been mainly used to wean adult patients off mechanical ventilation. Its use in pediatrics is gaining popularity. When used at our institution, we tend to keep a base line low SIMV rate (5 to 6 per min) along with pressure support before extubation.

CHAPTER

Commonly Available Ventilators

Praveen Khilnani

There are three fundamentally different modes of ventilation available in the pediatric intensive care unit (PICU) and the neonatal intensive care unit (NICU): "Pressure ventilators", "volume ventilators", and high frequency ventilators. They all serve to support adequate ventilation and oxygenation, but each has its own particular niche. There are different types of ventilators available in the market. It is obviously impossible to provide a detailed description of every ventilator in common use. These ventilators will be described with brief salient features. Author has no affiliation to any company or brand.

Volume Ventilators

Historically, volume ventilators (time cycled, volume regulated, volume limited) were used in anesthesia (a bellows of defined tidal volume pumped at a given rate) and as pediatric and adult intensive care evolved. Initially these ventilators were not used in the NICU due to the difficulty achieving consistent small volumes (5-7 ml/ kg in a 1200 g infant). Current volume ventilators are able to deliver small volumes consistently. In the past, triggering was inconsistent and increased the work of breathing. The latest generation (Baercub,Vela,Draager,Siemens 300 and servo i) has resolved these problems. In the NICU their use has been primarily in large infants with chronic lung disease (partly because SIMV (Synchronized intermittent mandatory ventilation) was only available on volume ventilators until recently or preoperatively (a tradition likely related to familiarity of operating room personal with volume ventilators). Their use in the acute NICU settings has extended into the micropremie population.

PROS: Stable minute ventilation with known tidal volume. Simpler models available for use outside hospital setting. Control or SIMV modes are available. Home ventilators currently available are typically "volume ventilators".

CONS: Tidal volume is maintained at the expense of peak airway pressure. If lung compliance falls by 50 per cent (i.e. Endotracheal tube, ETT slipping down right mainstem) then to maintain tidal volume, peak airway pressure doubles, possibly increasing the risk of volutrauma or barotrauma. Since these ventilators do not have constant flow, to breathe spontaneously the infant always has to trigger open a valve to allow airflow. Large leaks around the ETT can be problematic due to difficulty maintaining tidal volume and "triggering" (patient cycling) of the ventilator causing frequent alarming.

Pressure Ventilators

These are the most frequently used ventilators in the NICU. Traditional "pressure ventilators" are constant flow, time cycled, pressure limited devices (Sechrist ventilator). Constant flow implies that there is a constant flow of gas past the top of the endotracheal tube. Pressure limited means that once the pre-set PIP has been reached, it is maintained for the duration of the inspiratory cycle. Time cycled implies that breaths are given at fixed intervals, independent of the infants respiratory efforts. Newer "pressure ventilators" can sense infants breaths and synchronize with them. There may be some added work of breathing due to the need to trigger breaths this has been hard to quantify and remains controversial.

PROS: The constant flow permits the infant to easily take spontaneous breaths. Simple, reliable mechanical design. Pressure limitation prevents sudden changes in PIP (peak inspiratory pressure) as compliance changes (i.e. on a pressure ventilator if compliance falls by 50 percent PIP does not change–though tidal volume drops, for example ETT slipping down right mainstem). Leak around the endotracheal tube is compensated in a pressure ventilator by achieving preset pressure with whatever volume it has to pump.

CONS: Variable tidal volume as lung compliance changes, Should lung compliance worsen then Vt (tidal volume) will drop (if the ETT plugs Vt drops to zero, but the ventilator does not sense it). Should compliance improve (following surfactant for example) this may result in over-distention. If the child is exhaling during a non-synchronized ventilator breath, then the breath is ineffective.

High Frequency Ventilators

This is a radical innovation in ventilator design. The rate in "high frequency" is the Hz (range 3-15 Hz) (i.e. 180-900 breathe per minute). Since the tidal volume generated by these ventilators approximates dead space, simple pulmonary mechanics are not applicable.

High Frequency Oscillatory Ventilation (HFOV)

(Sensormedics 31OOA) uses a piston with diaphragm unit which actively move gas in and out of the lung. This type of ventilator requires a special non-complaint breathing circuit. Indications for use of high frequency ventilation are unclear but include:

1. Initial and subsequent ventilatory support in very low birth weight infant with respiratory distress syndrome.
2. Air leak (pneumothorax, pulmonary interstitial emphysema).
3. Failure of conventional ventilation (pre-ECMO (Extra corporeal membrane oxygenation) step) particularly in persistent pulmonary hypertension of the new-born, meconium aspiration syndrome, pneumonia, and pulmonary hemorrhage.
4. To reduce the risk of volutrauma and barotrauma when conventional ventilator settings are very high.

PROS: May allow gas exchange when conventional ventilation has failed.

CONS: Unclear which patients will respond and there is some risk involved in 'just trying". Switching ventilators on an unstable patient who is on conventional ventilation may result in clinical deterioration. The high airway pressures often seen with high frequency ventilation can be transmitted to the heart (particularly with compliant lungs) and result in impaired cardiac output requiring inotropes and/or volume boluses. HFOV makes turning patients, taking X-rays, or performing ultrasounds more complex due to the heavy, non-flexible tubing. Stopping HFOV for suctioning or administering nebulized medications may negate its benefit.

Specific Ventilators

Note: Each ventilator manufacturer has utilized specific names for mode functions of their specific machine that may not be identical with other machines. Generally speaking most manufacturers aspire for providing a universal ventilator for all agegroups, not yet achieved, however with increased sophistication in technology, pulmonary graphics facility is now available in most modern ventilators. Each user should familiarize oneself with manual knobs or touch screen, to start and set up the ventilator, achieve the initial settings of modes(A/C Assist control, PRVC or SIMV), rate (frequency), FiO_2, tidal volume/PIP, PEEP, Pressure support, inspiratory time(or I:E ratio), flow rate as well as setting of various ranges of alarms.

VELA VENTILATOR: VIASYS HEALTH CARE (USA)

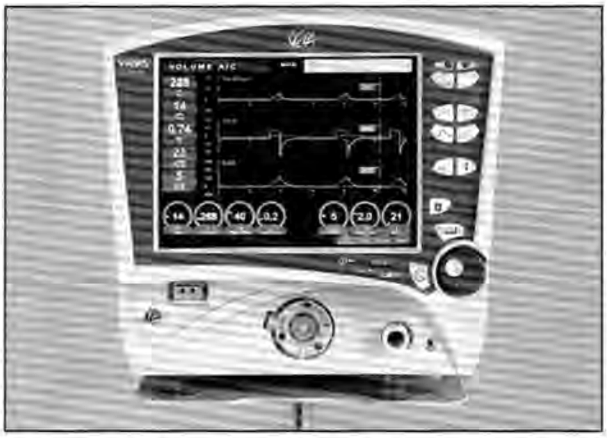

Fig. 35.1: VELA ventilator *(For color version see Plate 7)*

Features (as listed by the manufacturer)

Variable ventilation controls with integrated digital display for all controls and alarms with different color codes. Flashing display of controls available for any incompatible settings.

Front panel lock built into the control knob, to prevent accidental or unauthorised change of ventilation parameters.

Alpha-numerical window display for monitors, alarms, system messages and other informations.

Ventilator is self contained with built-in turbine (Air Supply) to run the unit independently without any additional Air or Oxygen Pressure Source.

Ventilator operates from AC, Internal Battery or optional External Battery Source. Display indicates the Power Source and different color codes available to indicate the charge status of the batteries.

Internal battery pack is standard and it takes over the unit automatically during power failure 2 hours. Batteries charging (internal & external) is automatic when it is used on AC source.

Basic machine has modes CMV, Assist CMV, SIMV and CPAP with independent Mode Selection Switches with PCV and Inspiratory Time. Peak flow ranges from 10-140 L/min for mechanical breath and upto 180 L/min for spontaneous breath. Flow Triggering is available along with bias flow settings ranging from 10-20 L/min. Pressure Support Ventilation is available in SIMV & CPAP modes. Inspiratory time range is 3.0 sec – 10 sec. Automatic flow calibration is available even when the ventilator is used on patient. Mechanical Over Pressure Relief valve is available as back up to High Pressure Limit Alarm for added safety to patient. Integrated nebulizer is available.

Monitored parameters include: Exhaled Tidal Volume, Spontaneous Exhaled Tidal Volume, Exhaled Minute Volume, Spontaneous Exhaled Minute Volume, PIP, MAP, PEEP, FiO_2, Total Breath Rate, I:E Ratio etc. Insp. Hold function is available for Static Lung Compliance measurement and display. Comprehensive Alarm package includes High Pressure, Low Pressure, Low Minute Volume, Low/High O_2 inlet pressure, Apnea Alarm and High Breath Rate.

Variable Apnea Backup ventilation is available whenever Apnea is detected.

Ventilator works from 100-240 VAC and has a sound level less than 50 dB including built-in turbine.

NEONATAL VENTILATOR MODEL BEARCUB 750 PSV–VIASYS HEALTH CARE (USA)

Fig. 35.2: Neonatal ventilator mode bearcub
(For color version see Plate 7)

Listed Features (from the manufacturer)

Microprocessor Controlled Time Cycle Pressure limited ventilator suitable for pre-mature babies, infant and neonates.

Ventilator have the following Modes of ventilation: Control, flow cycle assist control, SIMV/PSV, Flow-cycled SIMV, CPAP/PSV.

Respiration Rate upto 150 bpm with inspiratory time for 0.1–3.0 sec, PEEP upto 30 cm H_2O, inspiratory pressure upto 72 cm H_2O.

It has integrated electronic blender for O_2 sets from 21-100 percent.

Selectable apnea alarm ranging from 5 to 30 sec with apnea backup ventilator whenever apnea is detected.

Safety features viz volume limit which the maximum tidal volume of all breaths delivered by ventilator (Range of volume limit 5–300 ml).

It is able to monitor following parameters: Breath rate, inspired and Expired Tidal Volume, Inspiratory time, exp. time, I:E Ratio, peak insp. Pressure, mean airway pressure, PEEP, percent of tube leak, Air/ O_2 Pressure, Minute Volume.

Ventilator have comprehensive alarm package comprising of high breath rate, low PEEP/CPAP, low insp. Pressure, volume limit, apnea alarm, flow sensor, high pressure limit, low gas supply, minute volume alarm.

It is state-of-art ventilator from reputed company with CE and ISO 9001 Certification.

VENTILATOR MODEL AVEA- VIASYS HEALTH CARE (USA)

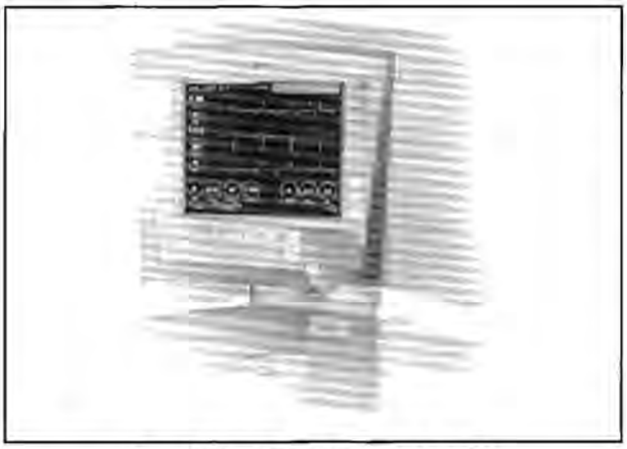

Fig. 35.3: Ventilator model AVEA
(For color version see Plate 7)

Microprocessor controlled time cycle pressure limited ventilator suitable for pre-mature babies, infant and neonates.

Ventilator have the following modes of ventilation: Control, flow cycle assist control, SIMV/PSV, Flow-cycled SIMV, CPAP/PSV.

Respiration Rate upto 150 bpm with inspiratory time for 0.1–3.0 sec, PEEP upto 30 cm H_2O, inspiratory pressure upto 72 cm H_2O.

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It is able to monitor following parameters: Breath rate, inspired and expired tidal volume, inspiratory time, exp. time, I:E ratio, peak insp. pressure, mean airway pressure, PEEP, percent of tube leak, Air/ O_2 pressure, minute volume.

Ventilator have comprehensive Alarm package comprising of high breath rate, low PEEP/CPAP, low insp. Pressure, volume limit, apnea alarm, flow sensor, high pressure limit, low gas supply, minute volume alarm.

It is state-of-art ventilator from reputed company with CE & ISO 9001 certification.

Drager Babylog 8000

This ventilator is specifically designed for infants up to 10 kilograms (22 pounds). It is capable or both volume and pressure ventilation. A flow sensor at the Y piece close to the patient accurately measures tidal volume and senses air flow initiated by the patient allowing triggering of the ventilator cycle. The sensor is able to compensate for small ETT leaks. High frequency ventilation can be delivered at 5-20 hertz.

The Drager Babylog 8000 provides the following modes: AC (assist control), SIMV PSV (pressure support ventilation), volume guarantee (VG), and independent expiratory flow. VG is often used with SIMV, PS and AC. The most important commonly used modes are SIMV, PSV, VG and CPAP (continuous positive airway pressure). This ventilator can also be used for non-invasive ventilation.

Fig. 35.4: Drager babylog 8000
(For color version see Plate 7)

Drager Baby log 8000 Controls (as listed by the manufacturer)

Conventional ventilation continuous flow, pressure-limited time-cycled

Triggered ventilation SIMV, SIPPV, PSV1), leak adapted

- Trigger Flow/volume trigger, leak adapted
- Trigger delay approx. 40-60 ms

High Frequency Ventilation1) CPAP+HFV, IMV+HFV

- Frequency 5 to 20 Hz

Volume Guarantee Ventilation1) SIMV+VG, SIPPV+VG PSV+VG

Oxygen mixer loss (bleed flow) 0 (zero) L/min

Settings

Inspiratory oxygen concentration 21-100 vol. percent oxyge

Peak inspiratory pressure 10 to 80 mbar

PEEP/CPAP 0 to 25 mbar

Maximal frequency 200 bpm
Inspiratory time 0.1 to 2 seconds
Expiratory time 0.2 to 30 seconds
Inspiratory flow 1 to 30 L/min
Base Flow (VIVE) 1 to 30 L/min

Monitoring

Flow monitoring at the Y-piece, integrated
Volume monitoring at the Y-piece, integrated
Lung function monitoring compliance, resistance C20/C
Method linear regression analysis
FiO_2 monitoring integrated
Real-time curves Flow and pressure, integrated
Inspiratory oxygen concentration 21-100 vol. percent oxygen
Peak pressure to 99 mbar
Mean airway pressure to 99 mbar
Graphic trends 6 parameters, integrated
Logbook record of up to 100 alarms
Notes: 1) optional available

Drager Babylog 8000 Plus, Evita XL, Evita 2 Dura

Fig. 35.5: Drager babylog 8000 plus
(For color version see Plate 8)

The Babylog 8000 plus is designed for harmonious ventilation of small children and the smallest preterm babies. It has an advanced upgrade platform that has allowed it to keep pace with all new forms of treatment and clinical advances. Sensitive synchronization with gentle but precise support for spontaneous breathing reduces the work of breathing and makes the ventilation process much more comfortable for patients. All of the above features of Babylog 8000 are available in Babylog plus.

Drager Evita XL is a newer model useful for pediatric, neonatal as well as adult age group . The Drager Evita 2 Dura Ventilator is used for adult and pediatric patients. Options include DC monitoring plus, ventilation plus, neo flow. Its features incl modes such as, Invasive - Volume-controlled mo assist/control - SIMV PSV - MMV and Pressu controlled modes, assist/control SIMV (PSV), CP BIPAP1 /PCV.

Siemens Servo 900C Ventilator

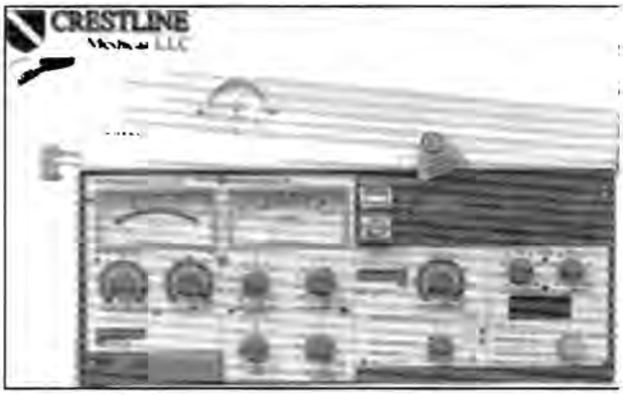

Fig. 35.6: Siemens servo 900C ventilator
(For color version see Plate 8)

It is either a volume or pressure ventilator, no flow from ventilator between breaths. It is volu ventilator with IMV, SIMV, AC and pressure mo PC/PS. It has pediatric settings for alarm limits, no specific infant modes. It is used when prima volume ventilator needed in larger term infant a Often for home ventilatory support. Currently, u only in the adult ICU. However, the servo ventila 900C can be used in intensive care and pati transportation, for adults, and older pediat patients.

Volume control: In volume controlled ventilat the inspiratory flow is kept constant as preset the Servo control System. As a result the tidal volu is also delivered as preset, and inspiratory time a pause time are maintained as preset.

Pressure control—efficient ventilation with l pressure.

Pressure control is a unique mode of the ser ventilator. By maintaining preset airway press constant throughout the entire inspiratory peri the servo ventilator delivers the tidal volume us a lower pressure level than traditional control ventilation.

Pressure control ventilation with constant ins ratory pressure gives you a decelerating flow w the major part of the tidal volume delivered in beginning of the inspiration and this prolonged time for gas exchange in the alveoli keeps lungs open with Pressure Control and Inverse I:E ratio.

Pressure controlled ventilation together with inverse I:E ratio is used to improve gas exchange and to prevent alveoli from collapsing during expiration. Using the inspiration time and pause time controls, the I:E ratio can be set from 1:4 to 4:1.

Siemens Servo 300/300A Ventilator

It can be used as a volume or pressure ventilator, with a low bias flow from ventilator between breaths. It does not have continuous high flow through circuit and requires some effort on the part of the infant to trigger significant flow. In the Neonatal Mode, there is a low continuous flow of 0.5 LPM through the circuit. A disruption of change in this flow caused by the infant's breathing is required to initiate/trigger an assisted breath. The major advantage over Siemens 900C is that it has infant ranges for Vt, flow, pressures, and alarms. It has extensive list of modes:
PC, VC, SIMV-VC+PS, SIMV-PC+PS, CPAP and PRVC (pressure regulated volume control). Uses include (1) volume ventilation of small infants, (2) synchronized/mixed modes, (3) overcoming resistance of circuit and ETT with PS, (4) facilitation of weaning by allowing gradual entertainment.

The servo ventilator 300 offers a wide range of ventilation modes for supported and controlled ventilation. It offers modes like PRVC (pressure regulated volume control) and VS (volume support) to deliver the required volume at the lowest pressure. Preset ranges for all relevant flow and volume parameters are automatically adjusted with a patient range selection knob. The servo ventilator 300 offers a wide range of ventilation modes for supported and controlled ventilation. The flow range covers very low flows from 0.1 ml/sec up to high flows of 3 L/sec.

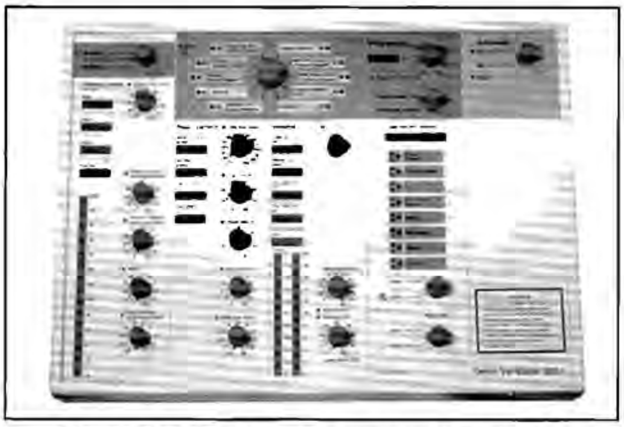

Fig. 35.7: Siemens servo 300/300A ventilator
(For color version see Plate 8)

Seimens Servo ventilator 300A is an improved version of Servo 300 ventilator.

Sechrist Ventilator (Old and Newer Versions)

This is continuous flow a pressure cycled time cycled ventilator.It has been commonly used for neonates with standard CPAP availability. Newer models are becoming available. The greatest advantage is absence of a demand valve to trigger ventilator cycle. Pressure support is not available in older models.

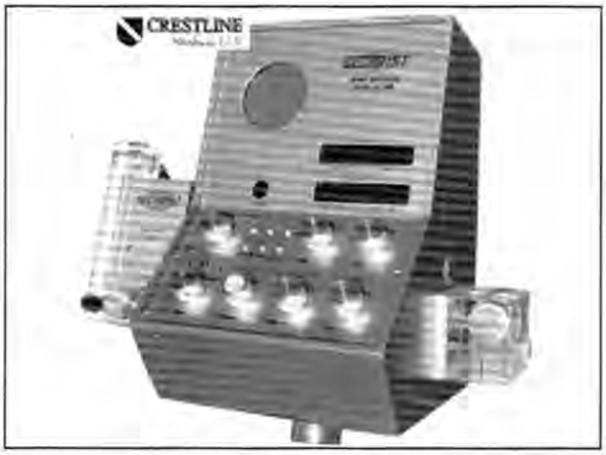

Fig. 35.8: Sechrist ventilator Old
(For color version see Plate 8)

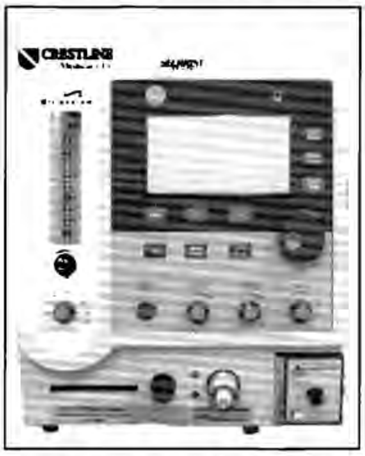

Fig. 35.9: Sechrist Ventilator New
(For color version see Plate 8)

VIP Bird Ventilators

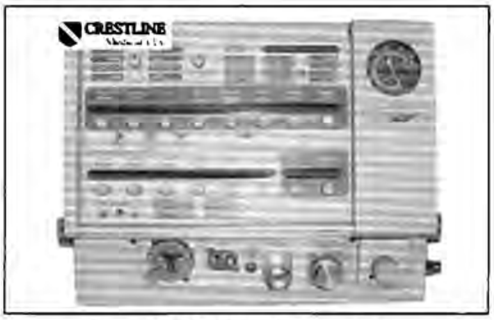

Fig. 35.10: VIP bird ventilator
(For color version see Plate 8)

Probably the earliest air driven ventilator with magnetic technology. Newer models have turbine technology alleviating the need for an air compressor to drive the ventilator. All modes are available for pediatric patients and small infants. A transport ventilator (BIRD AVIAN) is also available.

Transport Ventilator (BIRD AVIAN)

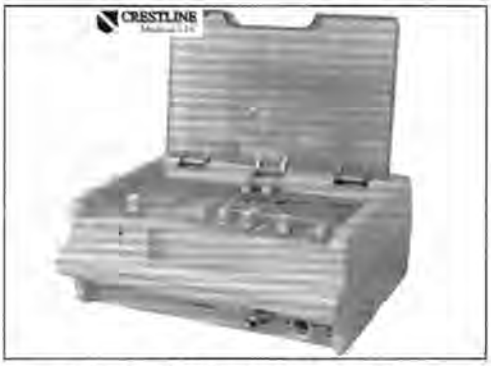

Fig. 35.11: Transport ventilator
(For color version see Plate 9)

Newport Ventilators: E IOOM, Breeze E150 and Wave E120 Ventilators

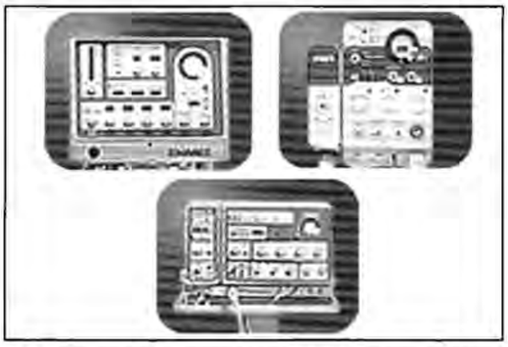

Fig. 35.12: Newport E 100m, Newport Breeze E 150, Newport WaveE120, Newport E 100M ventilator *(For color version see Plate 9)*

A relatively small size is the greatest advantage in being used as a transport ventilator.Delivers versatility, Value and performance according to the manufacturer. It can be cheaper to use in the PICU.

The Newport E100 M is designed to deliver reliability and versatility. It is ideal for most patient applications, eliminating the need for and expenses of age specific or application limited equipment. New advances, such as Advanced Trigger Control and Auto-Set Alarms, simplify the set-up and management of the ventilator. Duo Flow PLUS system allows to improve comfort, synchrony and work of breathing for spontaneously breathing patients.

These ventilators are available for pediatric intensive care unit, providing standard pressure, volume and time cycled nodes. PS is available, a unique flow triggering mechanism (bias flow and flow sensing) reduces work of breathing of a small child or infant making triggering easier.

Infant Star 500/950 Ventilator System

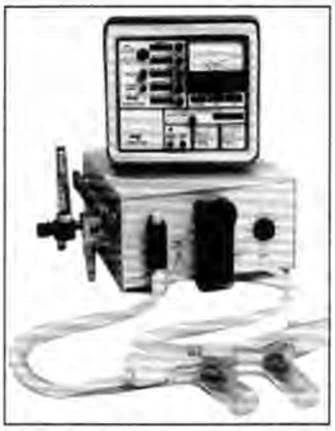

Fig. 35.13: Infant star 500/950 ventilator

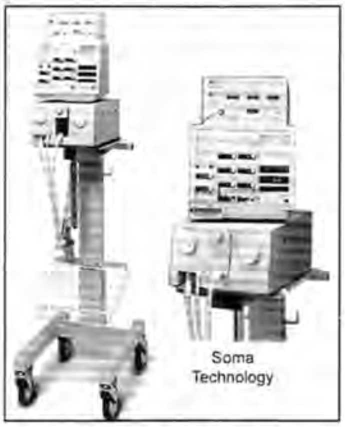

Fig. 35.14: Infant star 500/950 ventilator
(For color version see Plate 9)

The infant Star 500 and 950 ventilators are timed cycled, pressure limited, continuous flow ventilators, offering adjustable background flow in the CPAP and IMV modes. The infant Star ventilators are designed to provide continuous ventilatory support for neonatal and pediatric patients less than 40 lbs (18 kg), with an adjustable flow rate range of 4 to 40 liters per minute (L/min), and background flow range of 2 to 30 L/min.

Infrasonics Infant Star 950 is a high frequency ventilator with star cart. It has a flow interruptor for delivering high frequencies.The 950 Ventilator is timed cycled, pressure limited, continuous flow ventilators, offering adjustable background flow in the CPAP and IMV modes. Operations in the CPAP and IMV modes are identical in the 500 and 950 ventilators.

Siemens Servo-I (Maquet)

Fig. 35.15: Siemens servo *(For color version see Plate 9)*

Listed Features (from the manufacturer)

Supports neonatal and pediatric patients through multiple ventilation modes and sensitive triggering responses. Sensitive triggering and fast response times are important in preventing very young patients from "fighting the machine" and to ensure the delivery of safe, comfortable volumes. The pressure support mode of servo-I infant reduces the work of breathing and responds instantly to the child's changing needs. Treatment parameters and ranges can be flexibly customized and are automatically set, even when changing from one mode to another. The system can be upgraded to servo-I universal standard for all patient categories.

Fig. 35.16: Servo-i infant (Maquet) *(For color version see Plate 9)*

Product Benefits

- Automode for fully adaptive patient interaction.
- Lung recruitment for an even wider perspective of ventilation.
- Methodology and modes: the ability to explore different treatment strategies.
- Transportation with no loss of treatment quality.
- New generation of ventilators.

SERVO-i INFANT (MAQUET)

TECHNICAL SPECIFICATIONS

Parameter settings

Inspiratory tidal volume (ml): 5 – 350 *(Optional – together with volume related ventilation modes)*

Inspiratory minute volume(l/min):0.3 – 20 *(Optional – together with volume related ventilation modes)*

Apnea, time to alarm (s): 5 – 45

Automode Trigger timeout (s): 3 – 7

Pressure level (cm H_2O): 0 – (80 – PEEP)

PEEP (cm H_2O): 0 – 50

PEEP in NIV (cm H_2O): 2 – 20

CPAP pressure (cm H_2O): 2 – 20

CMV frequency (breaths/min): 4 – 150

SIMV frequency (breaths/min): 1 – 60

Breath cycle time, SIMV (s): 0.5 – 15

PHigh (cm H_2O): (PEEP +1) – 50

THigh (s): 0.2 – 10

TPEEP (s): 0.2 – 10

PS above PHigh (cm H_2O): 0 – (80 - PHigh)

PS above PEEP (cm H_2O): 0 – (80 - PEEP)
PS above PEEP in NIV(cm H_2O):0 – (32 - PEEP)
Back-up pressure above PEEP(cm H_2O):5 – (80 - PEEP)
NIV Back-up rate (breaths/min): 4 – 40
O2 concentration (%): 21 – 100
I:E Ratio: 1:10 – 4:1
TInsp (s): 0.1 – 5
NIV Back-up TInsp (s): 0.3 – 1
TPause (s) 0 – 1.5
TPause (% of breath cycle time): 0 – 30
Flow trigger sensitivity level
(fraction of bias flow):0 – 100%
Press. trigg sensitivity (cmH_2O): 20 – 0
Insp. rise time (% of breathcycle time):0 – 20
Insp. rise time (s): 0 – 0.2
Insp. cycle off (% of peak flow): 1 – 70
Insp. cycle off in NIV (% of peak flow): 10 – 70
Nebulizer time (min): 5 – 30
Parameter: Setting range
Oxygen breaths: 100 percent for 1 minute
Start breath: Initiation of 1 breath (In SIMV mode initiation of 1 mandatory breath)
Pause hold: Insp. or exp (0 – 30 seconds)
Alarm silence/reset: 2 minute silence and reset of latched alarms
Compliance compensation: On/Off
Automode (optional): Automode On/Off
Servo Ultra Nebulizer (optional): Nebulizer On/Off

Suction Support

Pre oxygenation time: Max. 2 min
Post oxygenation time: Max. 1 min
Suction phase time: No maximum level
Adjustable oxygen level: 21 – 100 percent

Saving of data

Recording of current waveform and parameter values: 20 seconds of data will be recorded (10 seconds before activated key and10 seconds after).Serial port: RS-232C - isolated. For data communication via the Communication Interface Emulator (CIE).
Network connection(optional):MIB (Medical Information Bus) monitorconnection
Data transfer Via Ventilation Record Card
Screen picture transfer: Via Ventilation Record Card

Sensormedics 3100A

It is high frequency oscillatory ventilator with active inhalation/exhalation driven by a moving piston and diaphragm.

The Sensor Medics 3100A High Frequency Oscillatory Ventilator was first approved for use in 1991 and is the only HFV approved for early intervention in the treatement of neonatal respiratory failure. The scope of application was broadened in 1995 to include selected pediatric patients failing conventional mechanical ventilation. The 3100A provides the ultimate in ling protection by inflating the lung with a continuous distending pressure and superimposing very small pressure and volume swings. Numerous publications, including clinical, animal and bench studies have reported improved benefit and outcomes asociated with the use of HFOV. There are over 3500 Sensor Medics High Frequency Oscillatory Ventilators in use worldwide today. The 3100A is the standard of care in more than 90 percent of Level III nurseries and 75 percent of the Pediatric Intensive Care Units in the US.

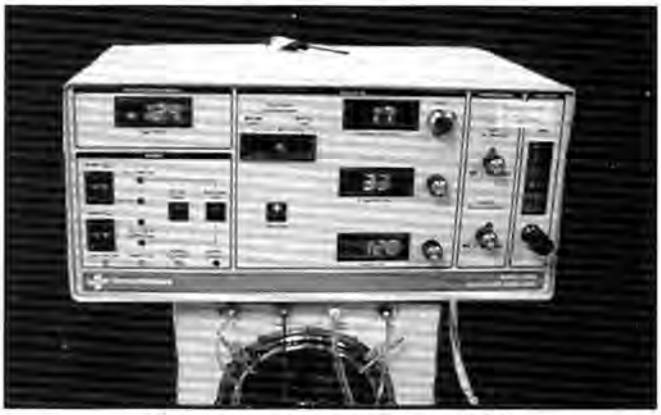

Fig. 35.17: Sensormedics 3100A
(For color version see Plate 9)

It requires special stiff non-complaint ventilator circuit. It can be utilized for a wide weight range of infants. Some preliminary work using it in smaller infants suggests that it may result in less barotrauma

Fig. 35.18: Sensor medics high frequency oscillatory ventilators *(For color version see Plate 10)*

than conventional ventilation. It is used extensively in western countries in severe Acute respiratory distress syndrome and meconium aspiration to avert the need for ECMO (See Chapter on High Frequency Ventilation).

Respironics BIPAP and Non-invasive Ventilator

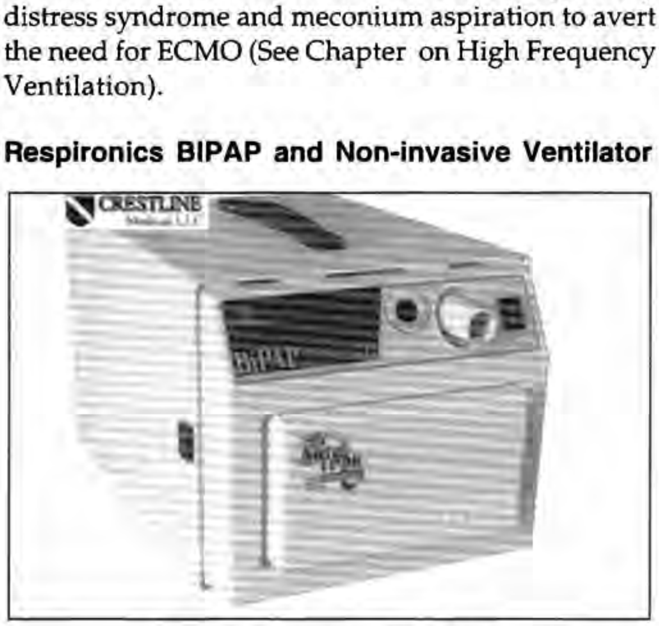

Fig. 35.19: Respironics BIPAP
(For color version see Plate 10)

A portable convenient device that can be used for non-invasive ventilation in the PICU.Circuit is supplied with various sizes of masks for pediatric use.Ventilator is capable of delivering, i PAP, e PAP and pressure supported breaths, shorter weaning times and increased patient comfort. Many brands of NIPPV are available.

Author's Comments

A ventilator with pressure control,volume control, wide range of tidal volume from neonate to adult, pressure support, SIMV, Assist control, CPAP, non-invasive ventilation capability (leak compensation), built in high/low pressure alarm, low tidal volume alarm, apnea alarm, power failure alarm with backup battery, low/high oxygen alarm, good humidification and warming system is desirable. Graphics, though optional are becoming a standard feature in most ventilators. SLE and Puritan Bennett ventilators have also become available in India in past few years. Reader is referred to product brochures for details.

Although all these ventilators have mostly proven satisfactory in use, most intensive care units will tend to use one make, so that nursing and medical staff can become familiar with the controls and monitors. Microprocessor technology makes it easy to adapt all these machines to encompass new ventilatory modes, but since there is no clear evidence that any one mode is superior to another it would also seem wise to restrict the problems of patient care and monitoring that are specific to each mode.

Company that provides cost efficient product, hands on training, good after sales service and a maintenance contract should be chosen for purchase of a ventilator.

It is also suggested that a user list be requested so the buyer can talk to the users and practical issues and with different ventilators can be discussed with current users.

High cost of ventilators is a big issue (In India , a ventilator may cost any where from 7 lakh to 18 lakh Indian rupees (15000 to 40000 US dollars) depending upon the company and product features). With newer Indian companies such as Shreeyash (Pune), ventilator technology is rapidly expanding in this part of the world to make cost effective ventilators (3-5 lakh Indian Rupees) that are clinically tested, available.

FURTHER READING

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CHAPTER

36

Advanced Mechanical Ventilation: Newer Modes and Modalities

Praveen Khilnani

Ventilatory strategies in the past evolved from surgical and anesthetic practice. In the immediate postoperative period, tidal volumes of 10 and 15 ml/kg ("sigh volumes") were used to prevent the microatelectasis that accompanied shallow or inadequate ventilation. In addition, blood gases were "normalized". It has become more apparent that this may place the injured lung at risk of further damage. Therefore, even more important than the technique or the machine, is the need to develop a strategy of treatment based on the pathophysiology.

Use of newer modes and different modalities of ventilation is rapidly evolving using a combination of following strategies.

- Using decreased tidal volumes (Vt) 7 ml/kg.
- Decreasing peak inspiratory pressure (PIP).
- Increasing inspiratory time (T insp).
- Using increased mean airway pressure.
- Washing out or bypassing deadspace.
- Permissive Hypercarbia and Hypoxemia.

In addition, other techniques may be used to meet other specific goals of:

- Treatment of asymmetric lung disease.
- Decrease work of breathing.
- Guaranteed tidal volume at lowest PIP.
- Lung rest.

Inverse Ratio Ventilation (IRV)

- *Strategy:* Decrease PIP increase (T insp) increase mean airway pressure.
- Inverse ratio ventilation is a technique first popularized by Reynolds in England, who applied this method to newborn with hyaline membrane disease. He reported better oxygenation and less barotrauma. This method became the forerunner of pressure-limited ventilation. Basically, it is controlled by positive-pressure ventilation with an inspiratory time ratio >1:1 or a duty cycle of >0.5. Duty cycle (Ti/Ttot) is the ratio of the inspiratory time (Ti) to the total breath cycle duration (T tot).

Inverse ratio ventilation can be established by any of the following methods:

a. Timed-cycled, volume-cycled, or pressure controlled ventilation with the inspiratory time (Ti) adjusted to the desired level,
b. Pressure-limited ventilation (either timed or volume-cycled ventilators) with a prolonged inspiratory time, or
c. Volume cycling with a prolonged inspiratory hold.

Improved ventilation reported with this technique probably results from increased duration of the inspiratory phase. This allows areas with longer time constants to receive greater flow than would otherwise occur with conventional volume-controlled ventilation with the usual I:E ratio. Improvement in gas exchange during inverse ratio ventilation is attributed to more effective alveolar recruitment and better distribution of ventilation during the extended inspiratory phase, thus decreasing deadspace ventilation.

The short expiratory time invariably induces intrinsic PEEP. Peak airway pressure (is lower than that with continuous positive-pressure) and increased functional residual capacity are responsible for the improvement in oxygenation.

Inverse ratio ventilation imposes a nonphysiologic breathing pattern and requires sedation or paralysis. There is often little effect on cardiac output at I:E ratio of < 4:1 in the volume repleted individual, but the occurrence of pneumothoraces may be as high as 25 percent. This may correlate more with length of time on inverse ratio ventilation than the I:E ratio or the mean airway pressure.

Inverse ratio ventilation is often used in patients with respiratory distress syndrome with refractory hypoxemia (PaO < 60 mm with an FiO, > 80%) despite the use of PEEP > 15 cm H_2O with CPPV. There are no controlled studies to show that inverse ratio ventilation reduces morbidity and mortality rates. In fact the beneficial effect is inconsistent and the exact role played by changing the 1:E ratio, as opposed to alterations in mean airway pressure or the incorporation of a decelerating inspiratory flow, is difficult to ascertain. It is possible that it is the absolute duration of inspiration that is the most significant feature in the apparent success of inversed 1:E ratio ventilation. Recently, East *et al*, reported on their success with the use of a computerized protocol for pressure control inverse ratio ventilation in patients with acute respiratory distress syndrome (ARDS). Their goal was to provide the highest mean airway pressure at the lowest PIP. They used FiO_2, and intrinsic PEEP values to determine oxygenation. The computerized protocol followed a specific algorithm for ventilator manipulations based on very appropriate physiologic strategies. They attained their goals with no apparent increase in barotrauma. Perhaps more importantly, it proved the feasibility of this protocol to allow for a more systematic approach.

Airway Pressure Release Ventilation (APRV) (Fig. 36.1)

Strategy: Decreased PIP increased (T insp) mean airway pressure.

Airway pressure release ventilation is a form of continuous positive airway pressure (CPAP) that releases the airway pressure from one preset CPAP level to a lower CPAP level. This allows a spontaneously breathing patient to exhale to a lower lung volume. The unique feature of airway pressure release ventilation is the augmentation of alveolar ventilation by a decrease in airway pressure and lung volume.

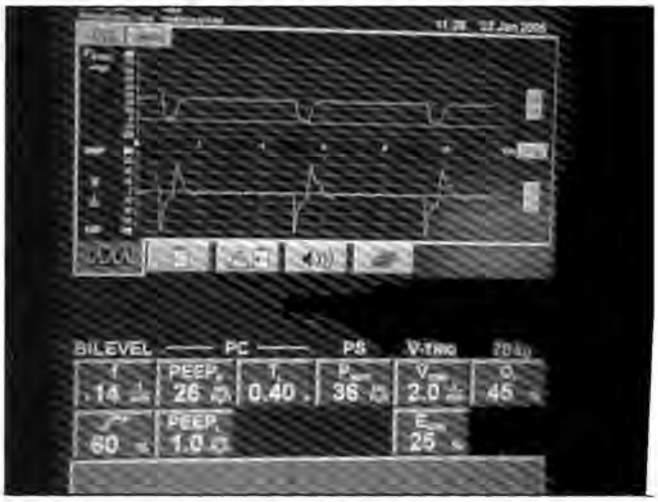

Fig. 36.1: APRV *(For color version see Plate 10)*

Preset variables are the initial CPAP level, th frequency of airway pressure releases (similar i concept, to intermittent ventilation (IMV), the lev to which CPAP reduces during release, duration the airway pressure release. The duration of th expiratory release (expiratory time) is usually < 1 sec. Peak airway pressure during airway relea ventilation is 30 to 75 percent that during CPPV ar may explain the finding that it has less of an eff hemodynamics than does CPPV. Peak airw pressure never, exceeds the CPAP level. Since airw pressure during airway release ventilation nev exceeds the CPAP level, it may be that inverse ra ventilation which reduces morbidity, clinica feasible to commence airway pressure rele ventilation in a patient receiving mask CPAP thera without the need for tracheal intubation.

Weaning occurs by lowering the freque airway pressure release, until the patient is breath with CPAP alone. From a synchronization sta point, augmentation of ventilation during air pressure release ventilation is similar to conventi IMV. Airway pressure release ventilation has been shown to significantly improve oxygenatio studies of humans with acute lung injury. It app more effective in improving alveolar ventilation oxygenation. It results in a lower $PaCO_2$ value conventional ventilation at a similar mi ventilation.

The rationale for the development of ai pressure release ventilation is similar to inverse ventilation, i.e. to open, maintain and stabilize the collapsed alveoli without peak airway pressure and the hazard of barotrauma. Thus, the initial CPAP level (or insulation pressure in inverse ratio ventilation) is responsible for stabilization of lung units and the expiratory phase is responsible for ventilation. Although the pressure tracings of inverse ratio ventilation with pressure limit closely mimic airway pressure release ventilation. The former usually has higher peak and mean airway pressures and doesn't allow for spontaneous breathing. In contrast to inverse ratio ventilation, airway pressure release ventilation allows the patient to breathe spontaneously between ventilator breaths, without requiring sedation and paralysis. In addition, the increase in functional residual capacity (FRC) in inverse ratio ventilation depends more on intrinsic PEEP because of higher closing volumes in children and CPAP levels that are often below critical opening pressure of airways, it is doubtful that airway pressure release ventilation will be useful for prolonged ventilation in children with acute lung disease. Further studies would be necessary as the indications for its use remain unclear.

Pressure Support Ventilation (PSV)

Strategy: Decreased work of breathing.

This is a patient-triggered, pressure-limited mode of positive pressure ventilation that delivers a preset positive pressure during the inspiratory phase (Fig. 36.2). Commonly, a pressure plateau is maintained until the patient's inspiratory flow decreases to a specified level at which time exhalation occurs. Unlike pressure limited ventilation, during pressure support the patient determines the initiation of inspiration, inspiratory times, flows and tidal volume, and the termination of inspiratory phase. The patients effort, the preset pressure limit, and the respiratory system impedance determines tidal volume (Vt). Inspiratory time and Vt can vary on a breath-to-breath basis.

Pressure support ventilation is reported to have many benefits. Most agree that it does compensate for the increased work of breathing due to the endotracheal tube and the ventilator demand valve. Improved synchrony between the patient and machine may help to explain the increased sense of comfort that pressure support ventilation provides. The most important physiologic aspect of pressure support ventilation may be its ability to better match the patient's inspiratory flow demands, thereby minimizing respiratory muscle effort as compared with other forms of mechanical ventilation. Pressure support ventilation should allow patients with mechanical impairment to ventilation to acquire larger inspiratory tidal volumes at the same level of effort or the same level of Vt at a lower level of inspiratory work.

Other benefits of pressure support ventilation include the reduction in the activity of the inspiratory muscles during spontaneous breathing. Values of 20 cm H_2O of pressure support ventilation abolish the pattern of electromyographic activity indicative of

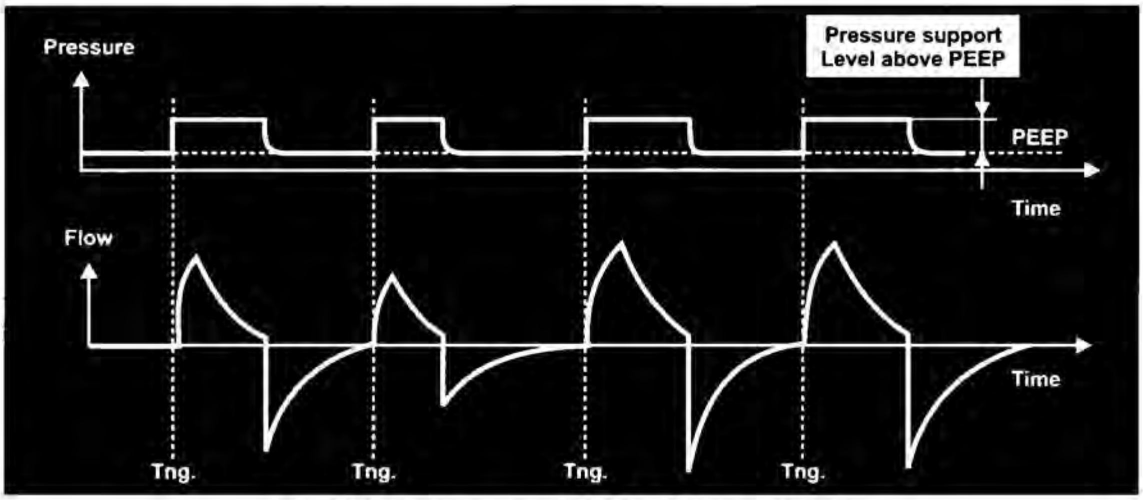

Fig. 36.2: Pressure support/CPAP: Pressure flowtrace

muscle fatigue. It may decrease oxygen consumption by the respiratory muscles and improve respiratory muscle loading while decreasing the respiratory muscle work per liter of ventilation as well as total muscular work per minute. Decreased intrinsic PEEP, elastic work of breathing, and oxygen cost of breathing have also been reported. Although not documented, some feel that it improves endurance conditioning of the respiratory muscles.

Proponents suggest initial ventilation at maximum pressure support ventilation. This is the level of pressure support required to produce a Vt of 10 to 12 ml/kg, and corresponds to the level where inspiratory work is least. Gradually, the pressure support ventilation level is decreased to < 10 cm H_2O (above PEEP), when extubation can be performed.

Since each breath must be initiated by the patient. Pressure support ventilation should be used with caution in patients with an unstable respiratory drive or highly changeable respiratory impedance (e.g. a patient with reactive airway disease). In the latter case, as with all forms of pressure-limited ventilation, as the patient's impedance changes, delivered VT may be affected. Synchronized mandatory ventilation (SIMV) and pressure support ventilation may be preferable when one requires complete mechanical support.

Pressure-regulated Volume Control (PRVC)

Strategy: Guaranteed Vt at lowest PIP and decreased work of breathing.

This is the new mode of controlled ventilation found on the Servo 300 ventilator (Fig. 36.3). It uses a decelerating flow generator (as used in the Pressure Control mode on the 900 C ventilator) as a pressure generator (pressure remains constant). The ventilator evaluates the exhaled volume on a breath-by-breath basis and will reset the pressure support level as needed to guarantee the Vt. The flow pattern often decreases the PIP (by approximately 5 to 7 cm H_2O) when compared with the same volume delivered in a volume control (constant flow) mode. Mean airway pressures may increase, averaging about 1 cm H_2O. Therefore, it overcomes the limitation of pressure support ventilation and mandatory minute ventilation by assuring a constant Vt, even with a lung with changing pulmonary mechanics.

Proportional Assist Ventilation (PAV)

Strategy: Decrease PIP and decrease work of breathing, increase volume of spontaneous breaths.

First described by Younes as a method to alter the mechanical load of the respiratory system, this method of positive pressure ventilation holds great promise for those patients with adequate respiratory drive. Essentially, the ventilator changes pressure at the airway in proportion to the inspired volume (elastic assist), the inspired flow (resistive assist), or both inspired volume and flow. The delivered volume or pressure varies according to the feedback signal the ventilator receives proportionate to the patient's elastic and/or resistive load. Thus, the ventilator simply reduces the total respiratory load and leaves the patient in total control of the breathing pattern. Conceptually, it is similar to the use of helium to decrease the respiratory load, or an intra-aortic balloon pump to decrease the load on the left ventricle. It also approximates what an

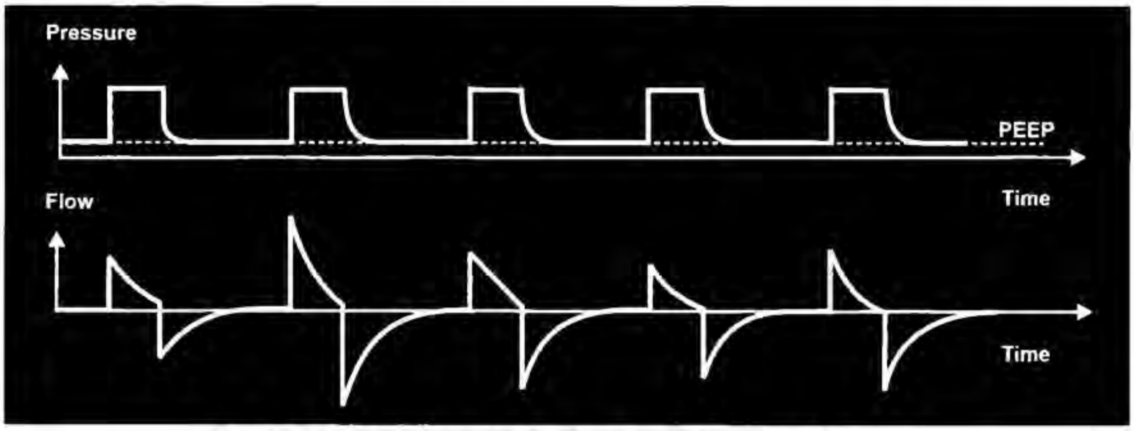

Fig. 36.3: Pressure regulated volume control: pressure flowtrace

individual may do while "hand bagging" a spontaneously breathing patient. As the patient takes a greater inspiration, the person bagging will squeeze the bag harder, i.e. the volume delivered will be proportional to the patient's inspiratory effort.

Nonconventional Techniques

These techniques represent a new approach to the management of patients with respiratory failure. Most of the techniques make use of very small Ventilators (Vts) or no Vts. Many studies suggest that these techniques can maintain adequate gas exchange under experimental conditions in which traditional concepts of gas transport no longer hold. Except for high-frequency ventilation, all the other modes attempt to decrease the respiratory frequency.

High Frequency Ventilation

High frequency ventilators may be classified by their exhalation phase. In one group of ventilators (such as the jet ventilator) exhalation is passive. In the other group, e.g. oscillators, the ventilator actively helps exhalation. Although there are many theories on how high frequency ventilation works, simple convection remains important despite the use of volumes often well below the deadspace volume. (Please refer to Chapter on High Frequency Ventilation).

Apneic Oxygenation

The application of apneic oxygenation involved ventilating an animal with 100 percent oxygen for 30 to 60 min to remove nitrogen from the lung. Then a source of oxygen was placed at the airway while the animal remained apneic. During the apneic period, $PaCO_2$ increased at a rate of 3 to 6 mm/min, the PaO_2 decreased from approximately 500 mm at about the same rate. Apneic oxygenation appears to have little clinical value in patients with acute lung disease, except as an adjunct with extracorporeal methods.

Tracheal Insufflation of Oxygen

This is a technique in which a constant flow of gas is insufflated into the trachea via a catheter placed near the carina. In apneic animals, oxygenation remained adequate but respiratory acidosis followed. In an animal model, tracheal insufflation of oxygen decreased both the $PaCO_2$ values and spontaneous minute ventilation. This technique appears to have limited clinical utility except, as with apneic oxygenation, as an adjunct with extracorporeal methods. It also may be helpful as a potential emergency procedure in patients with an airway that is difficult to intubate.

Constant Flow Ventilation

This is a method in which a constant flow of gas at a relatively high flow rate of about 1.5 to 3 L/min kg is insufflated through two catheters placed at the carina. During constant flow ventilation, the lung remains motionless, with sufficient airway pressure to maintain patency of airway and alveoli. Turbulence, molecular diffusion, cardiogenic and, most importantly, collateral ventilation seem to be important as the primary methods of gas transport with constant flow ventilation. Because of poor collateral circulation in humans, constant flow ventilation is largely ineffective for total alveolar ventilation. It is primarily a tool to study physiologic phenomena that are affected by breathing. However, Gilbert et al. reported on the use of a modification of constant flow ventilation for a patient with a bronchopleural fistula (BPF). He used constant flow ventilation in tandem with a conventional ventilator but only during the exhalation phase (intermittent flow expiratory ventilation). This allowed them to decrease the Vt on the conventional ventilator by one-third, thus decreasing the PIP significantly.

Liquid Ventilation (LV)

Ventilation with an oxygenated liquid perfluorochemical has been used experimentally in premature animals with respiratory failure. It has a high solubility for oxygen and CO_2 and a low surface tension. It has been shown to eliminate the interfacial surface tension improve distribution of pulmonary blood flow and support physiologic gas exchange without deleterious consequences when conventional techniques have failed.

More recently, Greenspan et al. tried this method in three human preterm neonates. Oxygenated perfluorochemical was allowed to flow into the patient's lungs by gravity for two 3 to 5 min cycles. Each cycle consisted of Vts of 15 ml/kg of perfluorochemical delivered over 5 seconds. Each Vt was held within the infant's lungs for 10 seconds and then allowed to drain by gravity. This was repeated at a rate of two to three liquid breaths per minute. After liquid ventilation, conventional ventilation and neonatal management resumed. Results showed that after a brief trial of liquid ventilation, two of the three neonates showed improved oxygenation and all three showed improvement in total respiratory compliance after return to gaseous breathing.

This physiology for perfluorochemical breathing has been previously described. After equilibration to 1 atm of pure oxygen, a perfluorocarbon may carry 45 to 55 ml dissolved oxygen per 100 ml solvent. During liquid breathing, the gel lining of the alveolus makes direct contact with the solvent, which is "inhaled and exhaled" in Vts (15 ml/kg). This eliminates air fluid interfaces and, thus, the resultant surface tension is eliminated. The compliance of the lung is dramatically enhanced, thereby eliminating the factors that cause maldistribution of ventilation in the surfactant-deficient lung. More recently, a perfluorocarbon was instilled in the lung at 30 ml/kg and used in tandem with mechanical ventilation. This was referred to as perfluorocarbon associated gas exchange. Documentation that it has advantages over conventional ventilation is lacking.

Altering Inspired Oxygen and Carbon Dioxide Concentration

A low alveolar oxygen tension increases pulmonary vascular resistance (hypoxic pulmonary vasoconstriction) and a high alveolar oxygen tension decreases pulmonary vascular resistance. With certain types of congenital heart disease such as hypoplastic left heart syndrome, it is critical to control pulmonary blood flow and prevent pulmonary flooding. One approach is to decrease the FiO_2 to less than 0.21 by blending room air with nitrogen. The exact FiO_2, delivered must be monitored to avoid administering, excessively low inspired oxygen. The other approach especially in mechanically ventilated patients, both preoperatively and postoperatively, is to increase the inspired carbon dioxide concentration ($FiCO_2$). Increased $FiCO_2$ also increase pulmonary vascular resistance. One of the difficulties with an increased $FiCO_2$ is increased spontaneous ventilatory drive as a result of an increased $PaCO_2$. This increases the work of breathing and with marginal cardiac reserve may impose undue strain on the heart. Therefore, increased $FiCO_2$ should be used judiciously, avoiding an increased work load on the heart in spontaneously breathing patients.

Helium-oxygen Mixture (Heliox)

Helium-oxygen mixtures have much lower density than oxygen-nitrogen mixtures and reduce resistance to air flow. This has been utilized in the properly successful treatment of upper airway obstruction after extubation in children. Helium-oxygen mixture has been used in upper airway obstruction due to laryngotracheobronchitis and postextubation subglottic oedema in infants and children. Helium is usually administered in at least 30 to 40 percent oxygen through a tight fitting facemask. Use of an oxyhood is not recommended, since helium tends to separate, and layer at the top of the oxyhood with the patient breathing very little helium. Recently, helium-oxygen mixture has been shown to improve gas exchange in neonates with respiratory distress syndrome. Oxygenation should be monitored during administration of helium-oxygen mixture to avoid hypoxia, especially in neonates. In adults helium-oxygen mixture has also been used in the management of severe lower airway obstruction in asthma Since the ventilator transducers are calibrated with air-oxygen mixture, the true volumes delivered tend to be different from preset values. Therefore when helium-oxygen mixture is administered through the ventilator, direct volume measurements are necessary to ensure that the appropriate Vt is being delivered. Heliox is not yet freely available in India

NAVA (Neurally Adjusted Ventilatory Assistance (Fig. 36.4)

Conventional ventilator technology uses a pressure drop or flow reversal to provide assistance to the patient. This is the last step of the signal chain leading to inhalation, and it is prone to disturbances such a intrinsic PEEP, hyperinflation and leakage. The earliest signal that can be registered with a low degree of invasivity is the excitation of th diaphragm. This signal is proportional to th integrated output of the respiratory center, and thu controls the depth and cycling of the breath. Th excitation of the diaphragm is independent o pneumatic influence and insensitive to the abov

INTRODUCING SERVO-i WITH NAVA
Neurally Adjusted Ventilatory Assist
MAQUET
18
4.7
1.2

Fig. 36.4: Naturally adjusted ventilatory assistance (*For color version see Plate 10*)

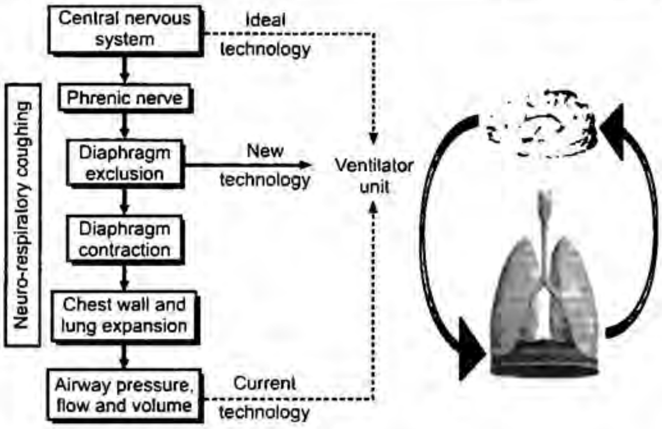
Central nervous system
Ideal technology
Phrenic nerve
Diaphragm exclusion
New technology
Ventilator unit
Diaphragm contraction
Chest wall and lung expansion
Airway pressure, flow and volume
Current technology
Neuro-respiratory coughing

Fig. 36.5: Respiratory control

problems with pneumatic triggering technologies. By following diaphragm excitation and adjusting the support level in synchrony with the rise and fall of the electrical discharge, the ventilator and the diaphragm will work with the same signal input. In effect, this allows the ventilator to function as an extra muscle, unloading extrarespiratory work induced by the disease process.

Asynchrony during SIMV-PS

The trigger delay from neural inspiration to the start of flow generation by the ventilator is typically about 100 ms with flow or pressure triggering. In a neonate with a total cycle time of 250-300 ms, this may constitute significant asynchrony while in an adult patient it may not be noticed. Continued insufflation during neural exhalation may pose a larger problem as this may aggravate hyperinflation, intrinsic PEEP and triggering delays.

NAVA

NAVA is independent of pneumatic disturbances and will provide respiratory assistance in full synchrony with the respiratory effort made by the patient (respiratory rate, duration of the breath and the tidal volume).The neural respiratory rate may be modified by the NAVA level. But synchrony will still be maintained.

The basic respiratory rhythm is generated by the respiratory center of the brain. The interval between bursts determines the respiratory rate and the intensity of the bursts determines the degree of activation of the respiratory muscles. The burst produced by the respiratory center travels along the the phrenic nerve and activates the diaphragm electrically. This excitation is captured by the electrode array of the Edi catheter and is transferred to the Servo-i, which delivers assistance to the patient in proportion to the signal obtained. Meanwhile the diaphragm signal induces the release of a neurotransmitter that directly activates the respiratory muscles. The subsequent shortening and descent of the diaphragm induce a drop in transpulmonary pressure below ambient, which is followed by inflow of air (Fig. 36.5).

Method

Parts needed for NAVA

- NAVA Software
- Edi Module
- Edi Module Cable
- Edi Catheter

Servo-i with NAVA

NAVA Ventilation Triggering on Edi Synchrony

Edi peak – The highest Edi value during one breath cycle

Edi min – The lowest Edi value during one breath cycle.

The electrical discharge of the diaphragm is captured through the introduction of a standard nasogastric tube fitted with an electrode array. Before the introduction of the catheter, the length of the catheter to be introduced into the patient is estimated by measuring the distance from the xiphoid process and up over the ear and to the tip of the nose. Make a note of the distance and place the catheter with this mark at the nostrils. By carefully following this instruction, satisfactory signal quality will be obtained in 95% of the cases. The nasogastric tube should be immersed in water for 5 minutes, which makes the catheter surface slippery. This avoids the need for other lubricants and assists in effortless introduction of the catheter. Insert the catheter with the previously estimated depth measured from the nostrils. Catheter position can now be checked by injecting a small amount of air and listening for bubbles with a stethoscope. Plug in the NAVA module to the Servo-i and connect the Edi catheter to its outlet. The Edi catheter positioning window of the Servo-i will assist in verifying proper Edi catheter positioning, through inspection of the esophageal ECG. A prominent P-wave should be seen in the uppermost channel with a continued decline of P-wave amplitude in the lower leads (Fig. 36.6).

As the diaphragm depolarization is captured, the signal is transmitted to the Servo-i which will deliver inspiratory support in proportion to the electrical activity of the diaphragm. In effect this provide extra muscle power and increases the efficiency of the respiratory muscles.

Benefits with NAVA

- Improve patient ventilator interaction: Synchrony by proportionally assisting each breath with minimum time delay.
- Enhance respiratory monitoring: Monitoring the electrical activity of the diaphragm (Edi). Information about the inspiratory drive and the brain signaling

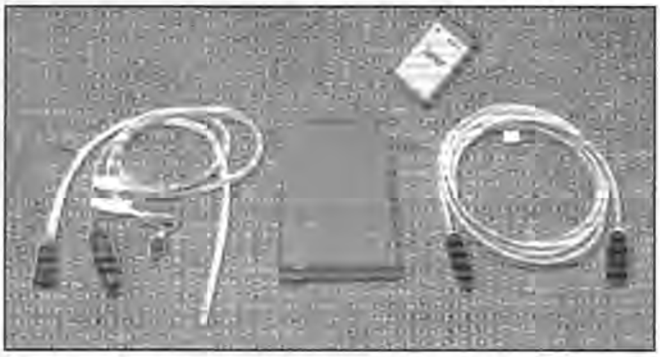

Fig. 36.6: Maquet (*For color version see Plate 10*)

- Reduce work of breathing: Missed trigger efforts do not exist. Intrinsic PEEP does not affect triggering.

Timely delivery of assistance

- Provide improved and safer ventilation: The patient controls the tidal volume. No run-away phenomena. Back-up function with mechanical triggering, pressure.

Support and Pressure Control

- Reduce need for sedation/paralysis: As a result of improved adjustments by the ventilator to the inherent breathing pattern, sedation can probably be reduced.
- Adapt to altered metabolic demand (e.g. fever): The proportional assist built into NAVA will compensate for altered metabolic demands resulting in increased amplitude of Edi.
- Prevent disuse atrophy: As the diaphragm is kept continuously activated diaphragm atrophy is ruled out.
- Shorten weaning time: Current experience shows that early extubation is possible with a higher degree of certainty as the decision to extubate is founded on knowledge both of the true respiratory drive and the degree of ventilator assistance and its effect on the electrical activity of the diaphragm.
- Improve non-invasive ventilation: As the pneumatic coupling is no longer critical for the trigger sensing, leakage is acceptable and will not result in autocycling.

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CHAPTER

Ventilator Graphics and Clinical Applications

Praveen Khilnani

Patients receiving respiratory support by mechanical ventilators need close monitoring in the pediatric intensive care unit, both for monitoring improvement or worsening in lung condition as well as for detecting and correcting potential problems leading to complications such as pneumothorax, hypoxemia, hypercarbia or rarely cardiac arrest.

Clinical monitoring of chest rise, breath sounds, color, oxygen saturation and the heart rate of the patient remain the best clinical parameters. In addition end tidal CO_2 monitoring and arterial blood gas monitoring is required.

The popular ways to monitor patients in most ICU are shown in Figures 37.1 and 37.2.

When checking the typical ventilator, the parameters examined are the Peak Inspiratory Pressure and the Exhaled Tidal Volume. The problem with these parameters is that we are only looking at two points in time (a zero mark and an end point).

By looking only at these two parameters, one will not be able to tell if the patient has sufficient flow, hyperinflation, air trapping, secretions, appropriate PEEP levels, or airway obstruction.

Pulmonary Monitoring with Graphics fills this gap. When using graphics, we see the entire breath from beginning to end. Ventilation decisions are made using thousands of points in time, not just two points in time. The graphics enable the clinician to see exactly what is going on in the lungs during mechanical ventilation.

The "art" of ventilation–evaluating clinically what the baby is doing and making changes in ventilation settings–is now being replaced by the "science" of ventilation–looking at data collected by respiratory

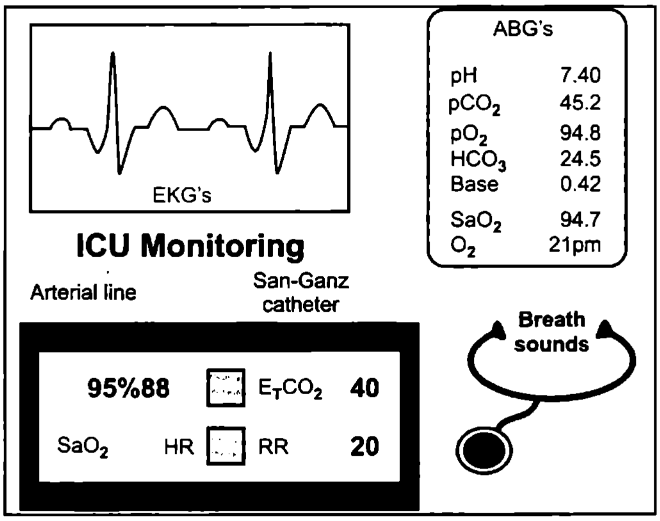

EKG's
ICU Monitoring
Arterial line
San-Ganz catheter
95%88
E_TCO_2 40
SaO_2
HR
RR 20
ABG's
pH 7.40
pCO_2 45.2
pO_2 94.8
HCO_3 24.5
Base 0.42
SaO_2 94.7
O_2 21pm
Breath sounds

Fig. 37.1

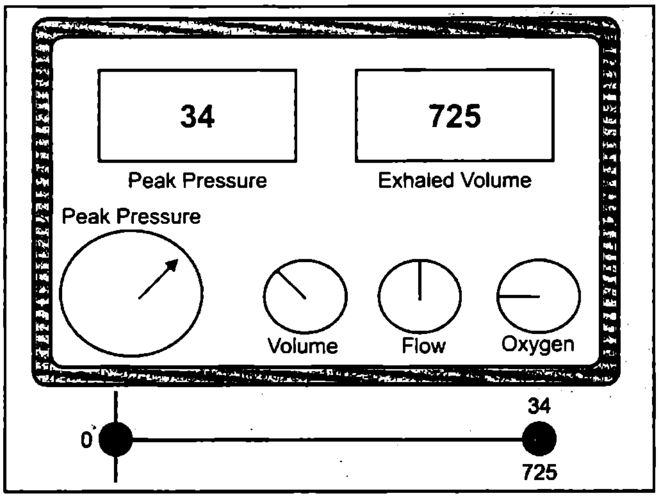

34
725
Peak Pressure
Exhaled Volume
Peak Pressure
Volume
Flow
Oxygen
0
34
725

Fig. 37.2

Figs 37.1 and 37.2: Methods to monitor patients in ICU function monitors and manipulating the ventilator accordingly.

With in line pulmonary mechanics monitor (now available on many ventilators) one can easily detect tube/circuit disconnection, tube obstruction, decreased lung compliance, brochospasm, patient ventilator dysynchrony, and auto-PEEP, and corrective measures can be instituted early to prevent potentially fatal complications.[1]

The use of noninvasive methods for the determination of the mechanical properties of the respiratory system in artificially ventilated patients has been advocated for the study of disease processes causing respiratory failure.

Knowing the mechanical properties of the lung and the dynamics of lung-ventilator interaction should allow the optimum matching of mechanical support to the mechanical need.

Rosen *et al*[2] showed the effects of bedside pulmonary mechanics testing during infant mechanical ventilation in a retrospective analysis. In 251 neonates ventilated with the help of pulmonary mechanics testing there was a significantly lower incidence of pneumothorax and intraventricular hemorrhage when compared to 217 neonates who were managed using similar ventilators without the help of pulmonary mechanics testing.

Fisher *et al*[3] have used pressure volume loops to identify and relieve lung distention during infant mechanical ventilation.

Although currently there are no studies available that directly show the effect of pulmonary function testing of ventilated patients on outcome in the pediatric intensive care unit, based on neonatal experience[4-6] the application of pulmonary mechanics may have significant impact on morbidity and/or mortality of mechanically ventilated pediatric patients.

In western pediatric intensive care units and some units in India, monitoring pulmonary mechanics with in line measurement at the level of endotracheal tube, is a routine part of monitoring respiratory functions on all intubated pediatric patients with respiratory failure, in addition to monitoring of pulse oximetry, end tidal CO_2, arterial blood gases and FiO_2.[7-9]

Mechanical ventilation thus becomes much more individualized, using graphics. It allows to adjust ventilator's settings to fit each patient's needs. Ventilation can become much more dynamic, because a patient's needs may change several times during his stay on a ventilator.

There are three basic parts to respiratory function monitoring. There are "waves"(scalars), "loops" and indirect measurements (that is, volumes, compliance, and resistance which are calculated by changes in the measurements in pressure and flow).Following are the definitions of the commonly used terminology when pulmonary mechanics are described.

Definitions

(a) *Airway pressure (P_{AW}):* Peak airway pressure is pressure required to deliver a given tidal volume at a given rate. P_{AW} is affected by flow resistive and elastic properties of lung and chest wall.

1. *Peak inspiratory pressure (PIP):* Pressure in the airways at the peak of the inspiratory pressure time waveform.
2. *Plateau pressure (Pplat):* Pressure in the airways after peak inspiratory pressure when inspiratory pause/hold is in effect,and effectively resistance of the endotracheal tube/upper airways/trachea is overcome. This is considered to be alveolar pressure, used to measure static lung compliance.
3. *Transpulmonary pressure* = P_{AW}-P_{ES} (pleural pressure). P_{AW} sampled at inlet of endotracheal tube represents proximal airway pressure.
4. *Transairway pressure (PTA)* = (PIP-Pplat) Reflects pressure required to overcome airway resistance. It increases in situations such as bronchospasm, increased secretions, mucus plug.
5. *Inadvertent (auto) PEEP:* Positive end expiratory pressure generated in the alveoli with air trapping during spontaneous or mechanical ventilation.

(b) *Flow (V) is defined as Volume of gas flowing across a given point per unit time.* Flow is affected by air passage resistance, viscosity, humidity, temperature and mix of gas.

(c) *Tidal Volume (Vt),* inspiratory and expiratory breath volume, is a function of gas flow and respiratory rate.

(d) *Esophageal pressure* (Pes) is measured by balloon catheter placed in midesophagus. Pes is used as a reasonable approximation of pleural pressure (PPI) in older children. In neonates with a distended chest wall Pes may not correlate with Ppl.[3-5]

(e) *Pressure Volume Curve* Airway pressure is plotted against tidal volume.

(f) *Flow Volume loop* Inspiratory and expiratory flow is plotted against volume.

(g) *Compliance (C)* is the measure of stiffness or distensibility (L/cm). Dynamic compliance (Cdyn) is tidal volume divided by total change in pressure required to deliver that volume. It is dependent on elastic (elastance and volume) as well as flow resistive (resistance and flow) properties of the lungs.

(h) *Resistance (R)* Pressure divided by flow (cm/L/sec).

(i) *Time Constant (TC)* Compliance X-resistance (sec). Time required to fill/empty an alveolus.
  - One Time Constant fills it 63%
  - Two Time Constants fill it 87%
  - Three Time Constants fill it to 95%

(j) *Work of Breathing (WOB)* Area under the pressure volume curve is equal to the work of breathing. Increased resistance increases the work of breathing.[10]

Technique of Respiratory Mechanics Monitoring[11-15]

In a mechanically ventilated child, flow/pressure transducer connected at the endotracheal tube connection with the ventilator circuit is an essential component of respiratory mechanics monitoring. Airway pressure (P_{AW}), as well as Flow can be accurately measured using this transducer. For measurements of compliance, resistance and time constant, an occlusion valve may be added to the ventilator circuit enabling pressure and volume measurements in addition to flow measurement.

An esophageal balloon catheter placed in midesophagus connected to the pulmonary function monitor measures Pes, which, in the absence of chest wall distortion, is considered in close approximation with pleural pressure (Ppl). Data from the transducer and esophageal balloon are processed by computer of the pulmonary function monitor and resulting pulmonary function parameters, e.g., *compliance, resistance, mean airway pressure and time constants can be printed.* Flow volume loops may also be obtained. The recorder display produces tracings of changes in airway pressure, esophageal pressure, airflow and tidal volume for each breath. Computer-assisted breath-to-breath studies can also be accomplished.

The flow transducer in line near the endotracheal tube measures two key variables:

- Airway pressure (P_{AW})
- Flow (V)
  - The addition of the occlusion valve to the circuit enables measurement of.
- Airway pressure (P_{AW})
- Compliance (Crs)
- Respiratory resistance (Rrs)
- Flow (V)
- Total resistance (RTS)
- Expiratory time constant

The addition of the esophageal balloon catheter with tip placed in midesophagus enables measurement of pleural pressure in children and adults. In neonates distortion of chest wall may affect the accuracy of esophageal pressure measurement.[16-18]

- Calculated parameters
- RR (Respiratory rate)
- PIP (Peak inspiratory pressure)
- PEEP (Positive end expiratory pressure)
- VE (Minute ventilation)
- Mean airway pressure (MAP)
- Peak inspiratory flow rate (PIFR) and expiratory flow rate (PEFR).
- Inspired and expired tidal volume.
- Inspiratory and expiratory time.

Ventilator Waveforms

Currently all new generation mechanical ventilators have incorporated a graphic display of ventilatory waveforms.[19-21] These waveforms have significant utility in managing patients on mechanical ventilators. A clinician at the bedside can obtain valuable information from the graphics. The primary benefit of ventilator waveforms is detection of any abnormality and taking corrective action.

Although relatively new, graphics have slowly gained popularity among clinicians in pulmonary medicine, these graphics illustrate theoretical concepts associated with pulmonary mechanics. In ventilator graphics, researchers in pulmonary medicine have found a reliable tool to provide justification for their findings.[22-24] Clinicians are expected to use these waveforms to improve patient management on mechanical ventilation.

Types of Waveforms[25]

There are two types of ventilator waveforms: **Scalars and Loops.**

Scalars are tracings of three parameters: **Pressure, Volume and Flow against time.**

These waveforms display patterns that have clinical significance.

Loops plot two parameters against each other: **Pressure vs. Volume** and, **Flow vs. Volume.**

Typical patterns of these loops are very useful in patient management.

Scalars

(a) *Flow vs Time (type of flow pattern):* Most ventilators allow the clinician to select a flow pattern that is most suitable for the patient (Fig. 37.3). Typically four types of flow patterns are available:

1. Square flow,
2. Descending ramp or decelerating flow,
3. Ascending rampor accelerating flow
4. Sine wave flow.

Observe that in each flow pattern illustrated on this frame the maximum flow rate is the same while Ti (inspiratory time)varies. However, if using a time-cycled ventilator the Ti remains constant and the flow varies to accomplish the preset VT.

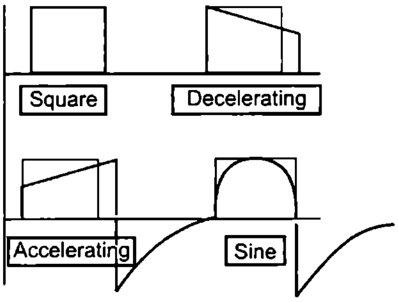


Fig. 37.3: Flow patterns

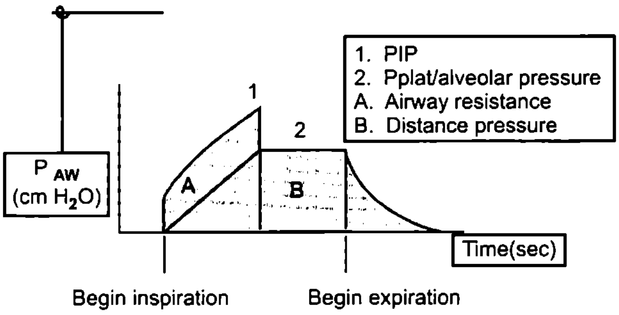


Fig. 37.4: Components of inflation pressure

(b) *Pressure vs. Time:* Clinically very important waveform.

Components of Pressure-time curve.

Although dynamic lung mechanics can be observed from a Pressure vs. Time curve, the addition of an inspiratory pause or inflation hold provides information to calculate static mechanics.

Plateau pressure (Pplat) or alveolar pressure is detected upon activation of an Inflation Hold or Inspiratory Pause control. The exhalation valve is kept in a closed position and the volume is held in the lungs. For clinical purposes, the plateau pressure is the same as the alveolar pressure. This measurement provides a means of measuring static lung compliance.

Transairway pressure (PTA = PIP – Pplat) reflects the pressure required to overcome airway resistance. Bronchospasm, airway secretions, and other types of airway obstructions are verified from an increase in the transairway pressure (PIP-Pplat) (Fig. 37.4).

With inflation hold, the clinician can determine the pressure required to overcome recoiling force (lung compliance). We can calculate static lung compliance by dividing the volume in the lung by the plateau pressure minus PEEP, if present.

$$\mathrm{Cs} = \frac{\mathrm{VT}}{\mathrm{P\ plat} - \mathrm{PEEP}}$$

Waveforms

Identify pressure and flow waveforms of volume controlled ventilation

Rectangular Flow Waveform (Square wave): Features: Highest Peak Pressure Lowest Mean Airway Pressure (Fig. 37.5.)

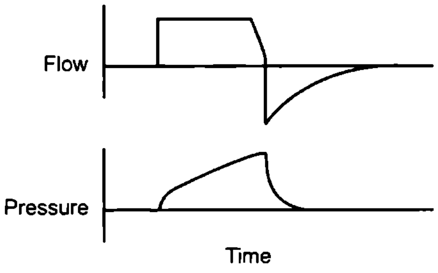


Fig. 37.5: Volume control—rectangular flow waveform

Descending Ramp Flow Waveform: Features: Lowest Peak Pressure Highest Mean Airway Pressure (Fig. 37.6).

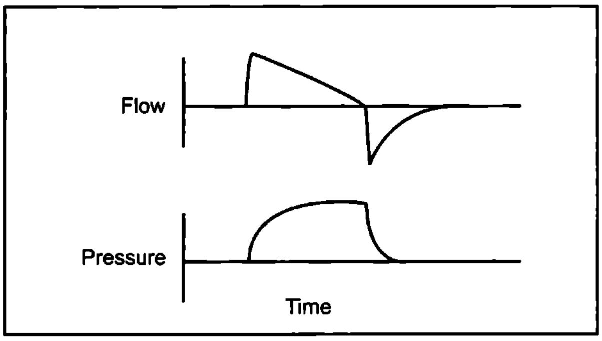


Fig. 37.6: Volume control—descending ramp flow waveform

Sine Flow Waveform: Features:Peak pressure less than rectangular waveform and higher than descending. Mean Airway Pressure is higher than rectangular waveform but lower than descending (Fig. 37.7).

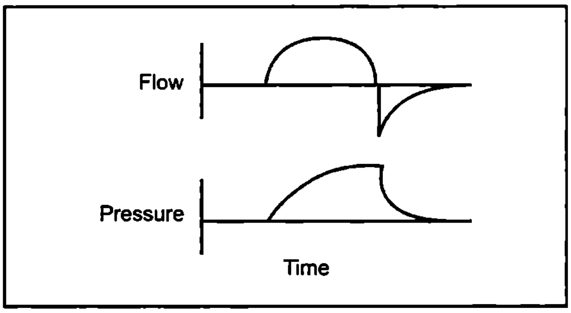


Fig. 37.7: Volume control– Sine flow waveform

In a normal lung tissue based on the airway resistance and compliance of smaller alveolar units there are fast alveolar units (Fast spaces), with low resistance, and normal or low compliance and slow alveolar units (Slow spaces) with high resistance and normal or high compliance.

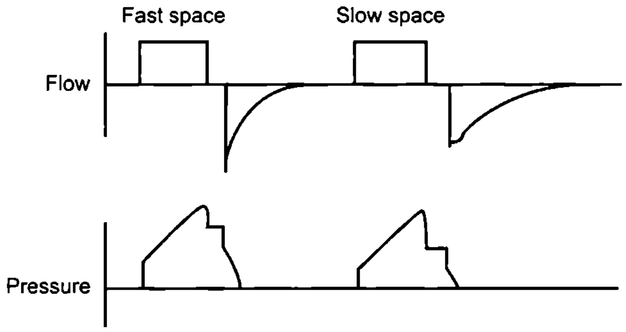


Fig. 37.8: Volume Control—rectangle flow waveform

Rectangular Flow Waveforms Comparing Fast and Slow Space Ventilation: Inspiratory flow wave remains constant. Expiratory flow takes longer to return to baseline with slow space. Plateau pressures are greater with fast space. The peak minus plateau pressure difference is greater in slow space due to the increased airway resistance and normal or increased compliance (Fig. 37.8).

Ramp Flow Waveforms Comparing Fast and Slow Space Ventilation: Changing to a ramp flow waveform lengthens inspiration and may cause air-trapping in slow space lung units. Expiratory flow takes longer to return to baseline during slow space ventilation. Peak and plateau pressures essentially equal each other in a ramp waveform since inspiratory flow has dropped to zero at end inspiration. Airway pressures are higher in fast space ventilation. The increase in airway pressure from high airway resistance in slow space ventilation is minimized with a ramp flow waveform (Fig. 37.9).

(c) *Volume vs Time:* Provides information on volume delivered to the patient. Components of a Volume vs. Time waveform. Information obtained from a Volume vs. Time scalar graph includes a visual representation of (Fig. 37.10):

- Inspiratory Tidal Volume
- Inspiratory Phase
- Expiratory Phase
- Inspiratory Time

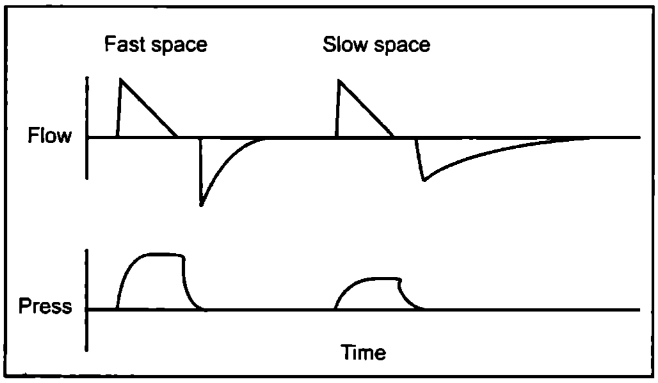

Fast space
Slow space
Flow
Press
Time

Fig. 37.9: Volume control—Rectangle ramp flow waveform

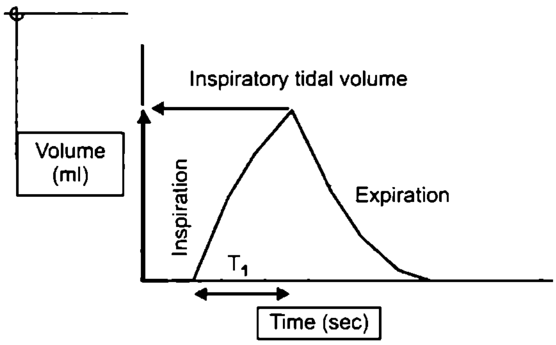

Inspiratory tidal volume
Volume (ml)
Inspiration
Expiration
T_1
Time (sec)

Fig. 37.10: Volume vs Time scalar

Certain conditions may be easier to detect viewing volume waveforms. The first graphic shows flow/time and volume/time waveforms of a volume controlled breath during normal function. The second graphic shows the same breath with a pause added (Figs 37.11 to 37.14).

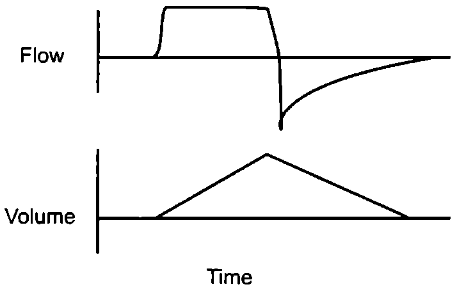

Flow
Volume
Time

Fig. 37.11: Volume control—rectangular flow waveform

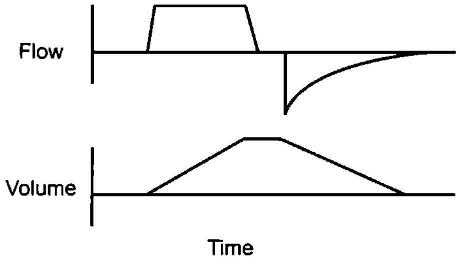

Flow
Volume
Time

Fig. 37.12: Volume control—rectangular flow waveform with inspiratory phase

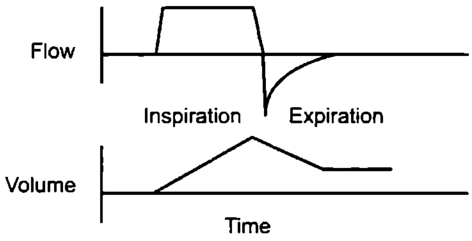

Flow
Inspiration
Expiration
Volume
Time

Fig. 37.13: Volume control– Rectangular flow waveform with a leak

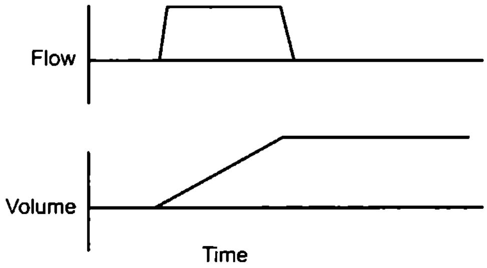

Flow
Volume
Time

Fig. 37.14: Volume control—rectangular flow waveform during a patient disconnection

The next graphic is an example of what a leak in the circuit would look like in a volume waveform. The last set shows a volume waveform during a patient disconnection.

Pressure waveforms can be used to adjust Flow-by. In Flow-by, the patient's inspiratory effort creates a drop in flow, rather than a drop in pressure, to trigger a breath. If the flow sensitivity and base flow are adjusted properly, there should be little, if any, drop in pressure when the patient triggers a breath.

LOOPS

(a) *Pressure-Volume Loop:* Clinically very important tracing

Components of a P-V Loop

A Pressure-Volume loop traces changes in pressures and corresponding changes in volume. Inspiration begins from the FRC level and terminates when the preset parameter (volume or pressure) is achieved. The tracing continues during expiration and returns to FRC at end of exhalation. PIP and delivered tidal volume are readily obtained from the Pressure-Volume loop.

(b) *Flow-Volume loop:* Detects abnormalities in flows associated with obstruction.

Components of a Flow-Volume Loop (Figs 37.15 to 37.17).

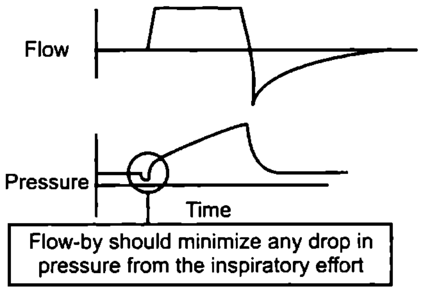
There is no set convention in assigning the inspiratory and expiratory quadrants on a Flow-Volume loop. Some ventilators produce flow-volume loop with inspiration on the upper quadrant and expiration on the lower quadrant. Other ventilators plot inspiration on the lower side of the volume axis and expiration on the upper side (Figs 37.18A and B).

A flow-volume loop provides the following information:

1. PIFR (peak inspiratory flow rate)
2. PEFR (Peak expiratory flow rate)
3. Tidal Volume
4. End of Expiration and Beginning of Inspiration

Clinical application of flow Volume Loop:

1. *Fixed upper airway obstruction:* Tracheal stenosis, undersized endotracheal tube, kinked or plugged endotracheal tube can be detected because both expiratory and inspiratory parts of the flow volume loop look flat, i.e. reduced flow during inspiration as well as expiration.



Flow-by should minimize any drop in pressure from the inspiratory effort

Fig. 37.15: Volume control—rectangular flow waveform with flow by and PEEP

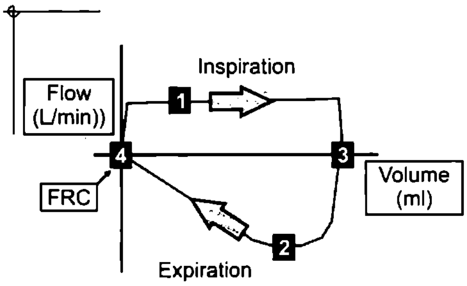


Fig. 37.17: Flow-volume loop

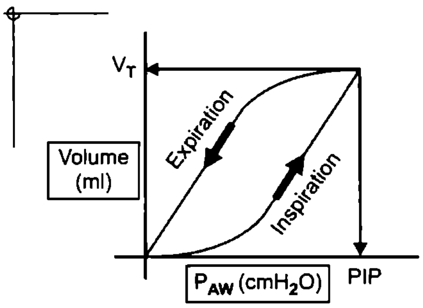


Fig. 37.16: Pressure-volume loop

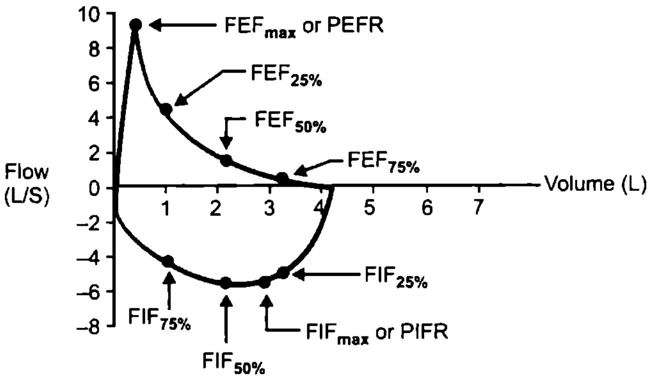


Fig. 37.18A: Flow volume loop on spirometry: Note the various points on the loop (FEF forced expiratory flow; FIF forced inspiratory flow; PIFR peak inspiratory flow rate; PEFR peak expiratory flow rate

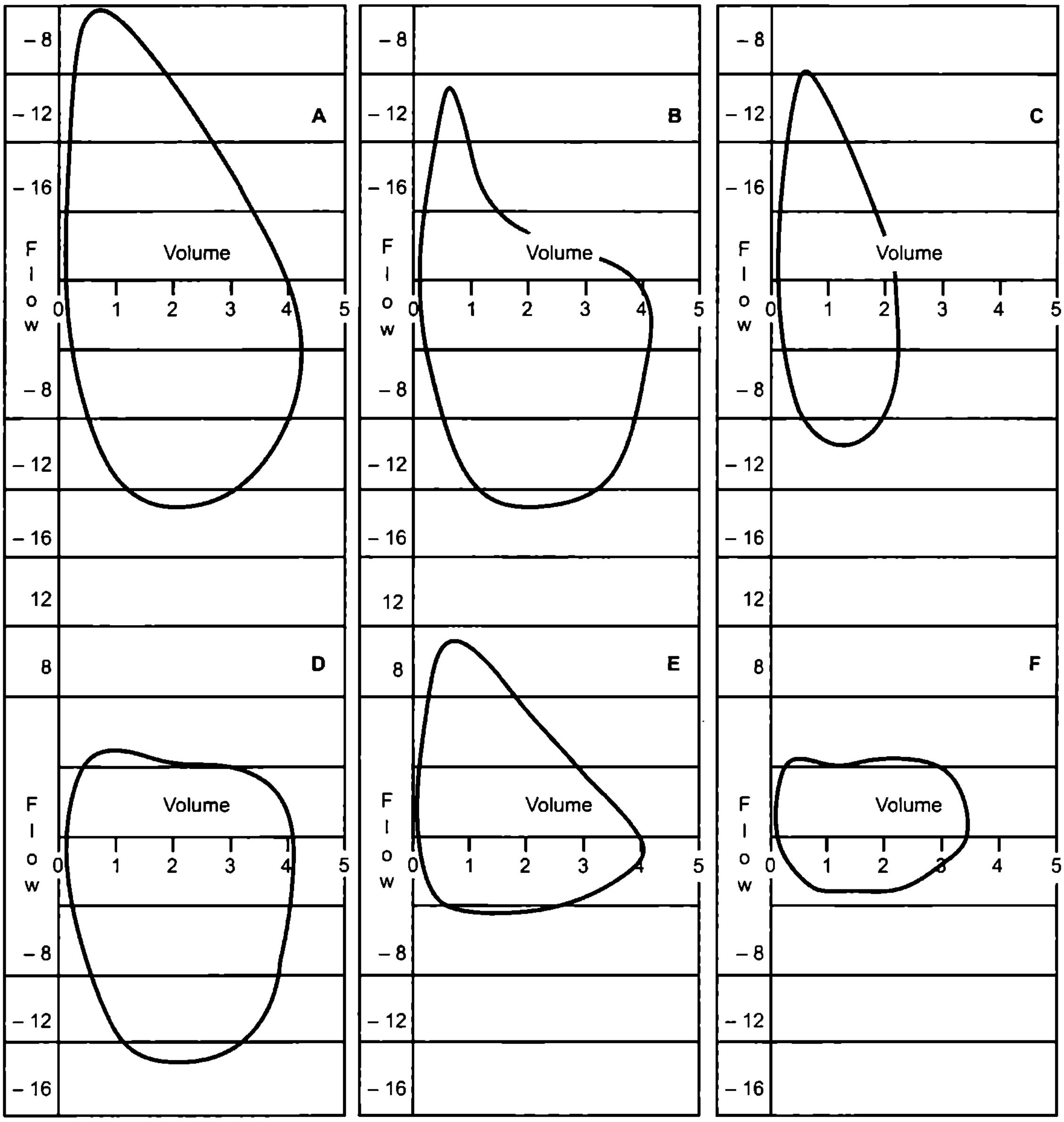


Fig. 37.18B: Characteristic flow-volume loops. A: Normal flow-volume loop; B: Patient with symptomatic severe asthma/cystic fibrosis; C: Restrictive lung disease, child with neuromuscular disease; D: Child with severe tracheomalacia (intrathoracic obstruction); E: Inspiratory flow limitation in a patient with vocal cord paralysis; F: Fixed obstruction in a patient with subglottic stenosis

2. *Variable extrathoracic obstruction:* Flat peak flow during inspiration.
3. *Variable intrathoracic obstruction:* Flat peak flow during expiration.
4. *Restrictive lung disease:* Decreased flow and tidal volume during inspiration.
5. *Asthma:* Decreased peak flow in maximal expiratory flow volume curve.

Flow/volume loops help in evaluating whether airway obstruction lessens after bronchodilator therapy. Improvement would result in a higher peak expiratory flow (top half). Keep in mind that these breaths are not forced exhalations. If there are higher expiratory flows from a reduction in airway obstruction, there would be less of a scooped appearance during mid to end exhalation (Fig. 37.19).

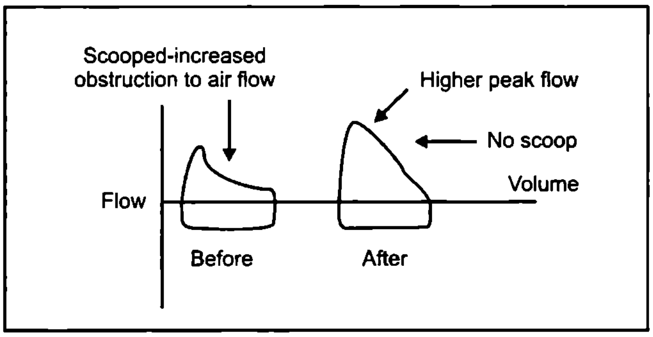


Fig. 37.19: FVL indicates positive bronchodilator response

ABNORMAL WAVEFORMS

Auto-PEEP or Air Trapping

Normally, expiratory flow returns to the baseline prior to the next breath. In the event that the expiratory flow does not return to the zero line and the subsequent inspiration begins below the baseline, auto-PEEP or air trapping is present (Fig. 37.20).

The presence of auto-PEEP or air trapping may result from:

a. Inadequate expiratory time
b. Too high a respiratory rate
c. Long Inspiratory Time
d. Prolonged exhalation due to bronchoconstriction.

Even though auto-PEEP is best detected from the flow-time waveform, its magnitude is not directly measured from the flow-time scalar. A higher inspiratory flow rate (in volume-cycled ventilators) or short Ti(in time-cycled ventilators) allows for a longer expiratory time and may eliminate auto-PEEP.

Increased Airway Resistance (Raw)

PIP vs. Pplat.

Changes in the pressure vs. time curve have notable clinical significance. Figure 37.21 illustrates four common clinical situations:

Normal curve: Indicates PIP, Pplat, PTA, and Ti.

High Raw: A significant increase in the PTA is associated with increased in airway resistance.

High Flow: Notice that the inspiratory time is shorter than normal, indicating a higher inspiratory gas flow rate.

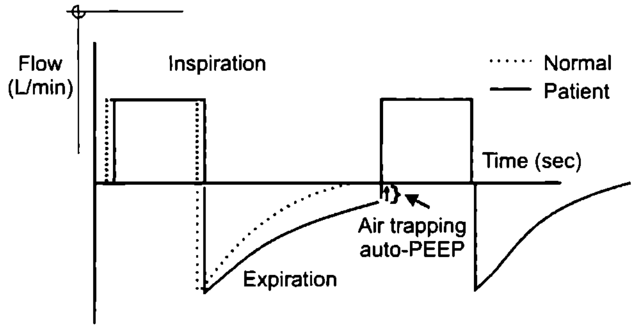


Fig. 37.20: Air Trapping

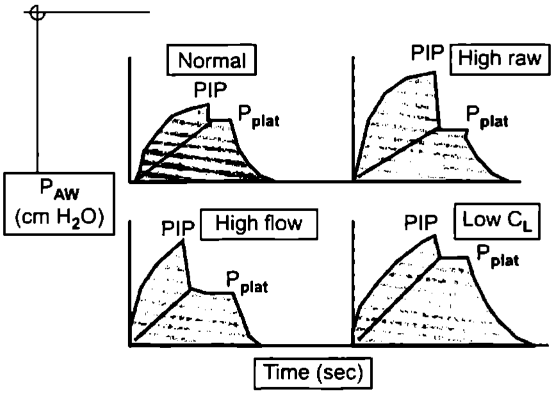


Fig. 37.21: PIP vs Pplat

Decreased Lung Compliance: An increase in the plateau pressure and a corresponding increase in the PIP is consistent with decreased lung compliance.

Decreased Lung Compliance during Volume Ventilation

A shift of the curve to the right of a Pressure-Volume loop indicates decreased lung compliance. A shift to the left is associated with an increased compliance. Observe the pressure required to deliver the same tidal volume in the three graphs. Higher pressure is required to deliver same tidal volume in a low compliance (shift to the right)situation (Fig. 37.22).

Alveolar Overdistension

Alveolar distension is a common observation made during ventilation of patients with ARDS on a volume-targeted mode. Alveolar overdistension is

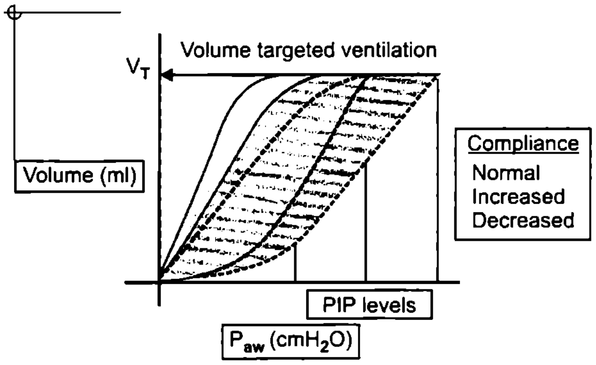


Fig. 37.22: Lung compliance changes in the P-V Loop

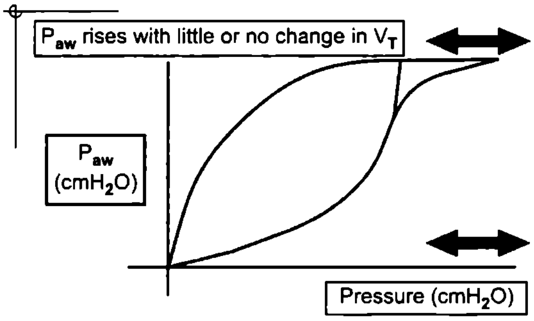


Fig. 37.23: Overdistension

detrimental to patients. The classic sign, known as "Beak Effect" or "Duckbill" shows an increase in airway pressure without any appreciable increase in volume. In this situation it is desirable to switch to pressure targeted ventilation at appropriate safe pressure level, or a reduction in Vt (Fig. 37.23).

Modes of Ventilation

Modes of ventilation are generally volume control or pressure control, and either of these modes will give clinicians the option of augmenting a spontaneous breath between the mandatory breaths by using pressure support. Mandatory breaths occur when either the patient or the machine triggers the breath to start and the breath itself is cycled into expiration by the machine. Spontaneous breaths occur when the patient initiates the breath and cycles the breath into expiration. Pressure-support ventilation augments the spontaneous breaths by adding flow (in a decelerating pattern) to reach a preset inspiratory pressure; this results in an increased tidal volume. Pressure support is available only in those modes that allow for spontaneous breaths. Positive end-expiratory pressure (PEEP) is one other common addition to volume-control and pressure-control modes.

Scalar Waveforms of Pressure and Volume Controlled Ventilation

Figure 37.24 shows a side-by-side comparison of the pressure-time, volume-time, and flow-time waveforms for volume-control versus pressure-control ventilation over four breaths.

Both examples show that the ventilator settings include 10 cm H_2O of PEEP, shown by the baseline tracing at +10 on the pressure-time waveforms.

On both tracings, the first and last breaths are mandatory, the first breath is time triggered, and the last three breaths are patient triggered (as seen in the triggering deflection on the pressure-time waveform). Pressure support of 20 cm H_2O is being delivered during the two spontaneous (second and third) breaths.

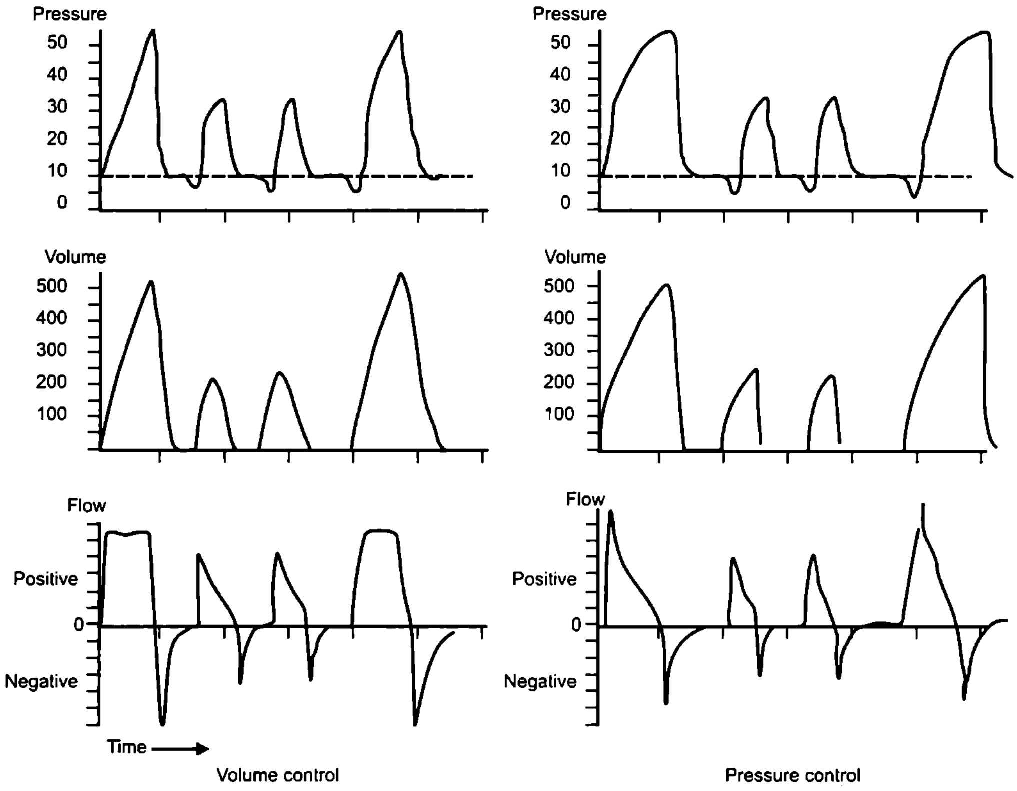
Scalar Waveforms during Common Modes of ventilation in Volume-Targeted Ventilation

a. Controlled.
b. Assist controlled,
c. SIMV (synchronized intermittent mandatory ventilation)
d. SIMV with pressure support

Note: A square flow pattern will be used to identify the inspiratory phase of the mechanical breaths in the Flow *vs* Time curve.

Controlled Mode

In a controlled mode the ventilator provides the entire breathing. The ventilator exclusively performs the work of breathing. The ventilator initiates inspiration when a preset time elapses (Time-triggered). It terminates inspiration when the preset tidal volume is delivered (Fig. 37.25).



Volume control

Pressure control

Fig. 37.24: Volume control vs pressure control ventilation over four breaths

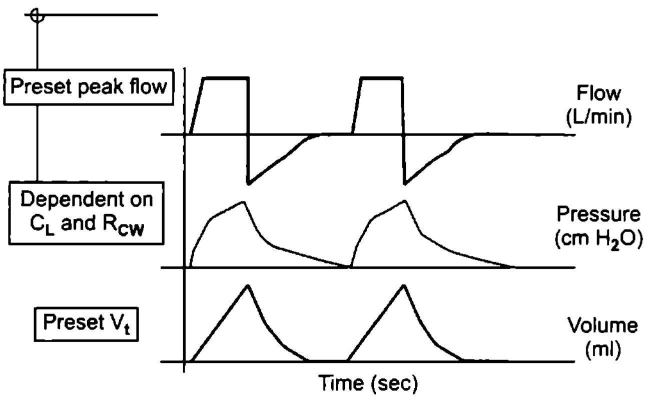


Fig. 37.25: Controlled mode (Volume-targeted ventilation)

Assisted Mode

An assisted mode is identical to a controlled mode except that the Pressure vs. Time curve shows a negative deflection just prior to the mechanical breath. This negative deflection indicates patient triggering (Fig. 37.26).

SIMV (Synchronized Intermittent Mandatory Ventilation)

This is the most common mode used in the clinical settings. It is primarily used to provide partial mechanical support. The patient's spontaneous breathing is supported with periodic assisted mechanical breaths (Fig. 37.27).

SIMV with Pressure Support (PS)

It is recommended that PS be added to SIMV to provide augmentation of unsupported spontaneous breath through the endotracheal tube.

Each breath is a patient triggered breath. Volume delivered during mechanical breaths is preset. However, the volume delivered by the Pressure Supported breath is dependent on the level of pressure support, patient's lung compliance, airway resistance, and patient's inspiratory effort (Fig. 37.28).

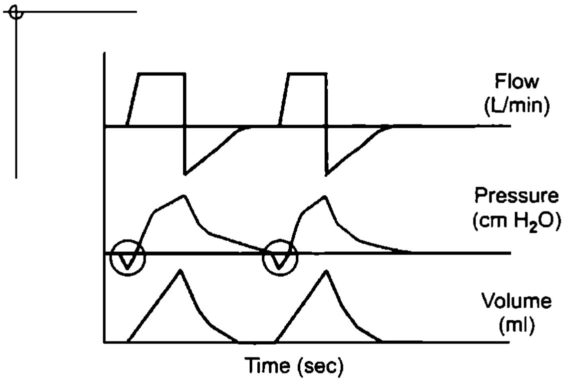


Fig. 37.26: Assisted mode (Volume-targeted ventilation)

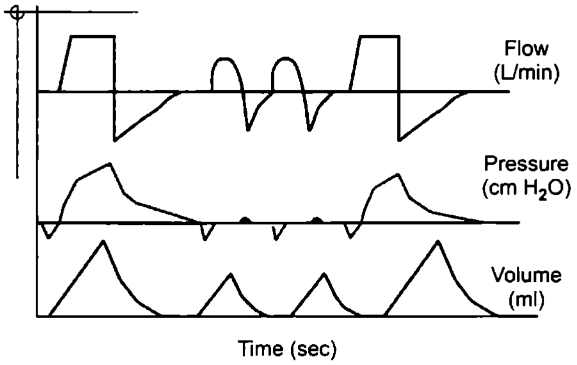


Fig. 37.27: SIMV—volume-targeted ventilation

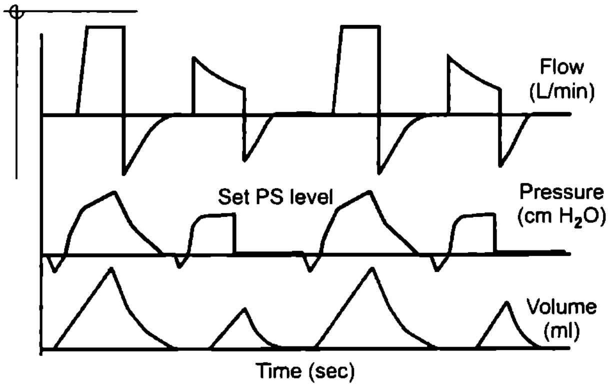


Fig. 37.28: SIMV + PS—volume-targeted ventilation

Clinical Applications and Significance

Clinical applications and significance of respiratory mechanics monitoring in mechanically ventilated patient can be following:

(a) Detect lung overdistension/prevent pneumothorax.
(b) Identify patient ventilator dysynchrony.
(c) Track rapid changes in tidal volume and compliance.
(d) Detect endotracheal tube obstruction, right mainstem intubation, bronchospasms and pneumothorax.
(e) Assess efficacy of bronchodilator therapy.
(f) Monitor tidal volume, minute ventilation for spontaneous as well as mechanical breaths.
(g) Other potential uses:
  1. Effectiveness of pressure support ventilation.
  2. Assessment work of breathing.
  3. Measure muscle strength by measuring maximal inspiration and expiratory pressures.

Conclusions

Graphics can aid clinicians in deciding which ventilator mode is most appropriate, or in fine-tuning the settings for a given mode in order to achieve the best combination for the patient. As the clinicians become more familiar with ventilator graphics, the more unusual and difficult waveforms and loops will be easier to understand and correct. Patient comfort and the effectiveness of ventilation are two important aspects of care that can be improved using the information provided by the graphics .Ventilator graphics constitute a valuable tool, and a thorough understanding of the associated patterns, problems, and corrections will help to provide high-quality, effective care.

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FURTHER READING

- "Essentials of Ventilator Graphics" an interactive CD created by Dr Ruben Restrepo and Vijay Deshpande. (www.respiratorybooks.com).

CHAPTER

38

Care of the Ventilated Patient

Meera Ramakrishnan

Care of a patient, especially mechanically ventilated patient, needs a team approach. In the western world and in some tertiary care centers in India, this team consists of the physician, the nursing staff, physiotherapists and respiratory therapists (RT). In majority of the centers in India however, there is no role played by physiotherapists or RT. Their services are usually provided by the staff nurse. Our nurses are often overworked and may be providing care for more than one patient. The cost of care in the ICU is also very high and hence needless procedures and practices are best avoided. It becomes imperative that we judiciously use the time of our personnel and follow as much of evidence based medicine possible. It came as a surprise to me that the majority of the practices that we follow in our day to day life in the ICU have very few trials, if any supporting its use.

This article will try to provide evidence for various practices such as humidification, positioning, physiotherapy, suctioning, nebulization as in an intubated patient.

Physiotherapy

Despite the extensive use of chest physiotherapy in pediatric practice there is very scant information available on its use in mechanically ventilated children. There is very little evidence for the beneficial effect of chest physiotherapy (CT). Its use is well established only in acute atlectasis and pediatric lung abscess in children greater than 7 years.[1,2,3] Prolonged immobilization and supine positioning leads to atlectasis especially of the left lower lobe, due to the weight of the heart. This in turn leads to retention of secretions super added bacterial infection and nosocomial pneumonia.

The physiological rationale behind CT is to mobilize secretions, prevent pneumonia and reduce hospital stay. CT consists of a series of maneuvers such as positioning, percussion, vibration and manual hyperinflation.[1,2]

Positioning

In order to increase drainage of secretion, improve ventilation/perfusion (V/Q) matching, improve oxygenation, decrease work of breathing and increase functional residual capacity (FRC) certain body positions are utilized in the ICU. These include the upright posture in a person who has obesity, ascites, abdominal surgery, or the 45° angle to decrease the risk of aspiration in a person being enteraly fed.

A person with unilateral lung disease is to be placed with the affected lung uppermost in order to improve drainage of secretion and also for a better V/Q matching[4] (as both perfusion and ventilation will increase in the gravitationally assisted normal lung).[1,2,5] One should however remember the risk of suppurative secretions draining into the normal lung and worsening the disease process. Prone positioning has been shown to improve oxygenation in up to 85 percent of patients in the early stages of ARDS by increasing FRC, increasing V/Q matching, enabling drainage of secretions and improving lymphatic drainage.[6-9]

Percussion and Vibration

Percussion is performed by manually clapping the chest wall using cupped hands.[3,10] It is done to mobilize secretions from the nondependent areas of the chest to the central airways from where they may be suctioned. Vibration and percussion can be done mechanically as well. Vibration is generally used in neonates to avoid damage to their fragile chest walls.

Manual Hyperinflation

It is usually performed before and between suctioning to prevent hypoxemia while suctioning. The patient is disconnected from the ventilator and is bagged with a resuscitator bag using slow deep inspiration, inspiratory hold and quick release to enhance expiration. This causes the recruitment of atlectatic segments and also mobilizes secretions.[1,2]

Continuous Rotational Therapy

This involves the use of specialized beds that continuously turn the patient along a longitudinal axis.[1,10] It is currently unavailable in India.

Fiberoptic Bronchoscopy (FOB)

This is used for removal of retained secretions and for suctioning thick tenacious mucus plugs. Despite its widespread acceptance for removal of secretions, its superiority over chest physiotherapy has not been proven. Despite this, one should consider FOB in lobar or greater atlectasis in patients not responding to vigorous chest physiotherapy or in life-threatening whole lung atlectasis.[11]

Complications

Chest physiotherapy is associated with increased incidence of hemodynamic disturbances, higher incidences of gastroesophageal reflux,[1,2] elevation of intracranial pressure and increase in oxygen consumption.[12-14] To some extent the effect on intracranial pressure and hemodynamics can be decreased by prior sedation and paralyzation of the patient. The head down positioning while doing rigorous physiotherapy is likely to increase the risk of aspiration and worsening of intracranial pressure. Neonates and children with fragile bones, such as in rickets and osteogenesis imperfecta, can deve rib fractures.

Currently there is very little data supporting using of CT for any condition outside of atlecta Positioning is useful in ARDS and in individuals w unilateral lung disease. Studies, however reveal t continuous rotational therapy and kine percussion[10] decreases pulmonary complicatio Studies done in adults show that chest phys therapy fails to decrease the length of hospitalizati length of fever[1] or duration of ventilation. Desp the rationale for its use CT has not been shown hasten the recovery from pneumonia or decrea the duration of hospitalization.[15]

Humidification

Normally the upper airway of a person heats a humidifies the atmospheric air to body temperatu and 100 percent relative humidity. Medical gas have no humidity and bypassing the upper airwa as in patients with artificial airway such endotracheal tube or tracheostomy makes humidi cation a must.[16,17] Decrease in the humidity can lea to mucosal damage and tube occlusions, atlectasi loss of FRC, hypoxia and increased incidence pneumonia. Excessive humidification is also problem and can decrease mucociliary clearanc cause hyper hydration and loss of surfactant activit Humidification can be achieved using heated wate humidifier (HW),[16,17] heated wire or by Heat an Moisture Exchange (HME) filters. The appropriat temperature and humidity to be used in ventilate patients has not yet been established.

Heated Water Humidifier (HW)

Heated humidifiers use heating elements to increas the temperature of water and humidity of th inspired gas.[18] The degree of humidification of th inspired gas will depend on the temperature setting flow rate, water level in the humidifier and th length of the circuit. These generally bubble th inspired gas through the column of water. These are to be used only with a high flow system such a that needed during mechanical ventilation. Th temperature of the inspired gas has to be monitore in order to avoid over heating and tracheal burns.

Heated Wire Circuit

In an attempt to decrease the rainout associated with heated water humidifier, heated wire circuit is available. This is available in both reusable and disposable form. The temperature of the gas is maintained at a select value.

Heat and Moisture Exchangers (HME)

HME filters combine humidifying properties[19,20] of plastic foam impregnated with hygroscopic substance, with bacterial filtering properties of filter membrane. HME filters are made of substances with low thermal conductivity such as ceramic, polyurethane, polyethylene or cellulose sponge material.[21] The hygroscopic substance can be Calcium Chloride, Magnesium Chloride, Aluminium Chloride or Lithium Chloride.[19] It chemically absorbs water vapours in expired gas, which then saturates the inspired gas. HME has been found to provide safe and adequate humidification of inspired gases. Some of the filters available in the market claim to be 99.5 percent efficient in its filtration properties. A recently done study, however, casts doubts about this claim. Their use, however, is associated with lesser circuit contamination. There has not been any statistical difference in the incidence of ventilator associated pneumonia (VAP) with the use of HME filters. Its use can increase deadspace and resistance, which may be overcome by increasing pressure support. It can be used safely up to a week[20,22] or until visible liquid contamination occurs. This gets converted to cost saving on disposables, fewer need for breaking the circuit and hence reduction in bacterial contamination.

Aerosol Therapy

Aerosol is a group of particles suspended in air for a relatively long time. Aerosol therapy is used in order to deliver the drug directly to the site of action, thereby minimizing the systemic side effects and improving the efficacy. The size of the aerosol is expressed as mass median aerodynamic diameter (MMAD). The MMAD determines the rapidity with which the aerosol will settle in the airway. Aerosol gets deposited through the process of impaction, sedimentation and diffusion.[23,24] In order to be maximally effective the aerosol particles should be 0.5-5 µm in size. Particles larger than 3 µm get impacted by its size on the tubing and endotracheal tube. Particles around 2 µm get sedimented due to gravity and still smaller particles undergo diffusion.

Aerosol therapy may be provided using nebulizers or Meter dose inhalers (MDI). MDI's are as efficient and according to some studies more efficient than nebulizers. The latter, however, has a greater versatility and can be adapted to deliver various drugs.

An array of drugs like bronchodilators, steroids, antibiotics, anticholinergics, mucolytics, prostacyclin etc. gets delivered by the nebulizer route. The most common drug however is bronchodilator and steroids.

The amount of the drug deposited in the lower airway will depend on several factors such as physiochemical properties of the drug,[23-25] the nature of the device, position of the device in the circuit, the nature of the ventilator circuit, ventilatory parameters, humidity and density of the inspired air and on the airway anatomy.

Characteristics of Aerosol Generating Device

Greater respiratory tract deposition occurs when the MMAD of the aerosol is in the range of 1-3 mm. The larger size particle can get impacted in the endotracheal tube and in the ventilator circuit.[23,26] A nebulizer could have continuous or intermittent operation. Continuous operation requires the nebulizer to be driven by a pressurized gas source. Intermittent operation requires a separate line from the ventilator to drive the nebulizer during inspiration. Between the two, intermittent operation during inspiration is preferred as it lowers the wastage of drug.

Ventilatory Parameters

Adequate aerosol delivery is achieved in assisted modes of ventilation only if the patient is in synchrony with the ventilator. 20 percent more delivery can be achieved during CPAP mode than with volume cycled breaths.[23,27,28] The tidal volume has to be higher than normal to compensate for the compressible volume of the tubing. Longer inspiratory time has to be used in order to increase the nebulizer generated aerosol to be inhaled with each breath. This is needed even in an MDI generated aerosol although the mechanism is not clearly known.

Circuit Characteristics

In general, smaller endotracheal tube, narrow internal diameter of the pediatric ventilatory circuit and humidification of gases[1,29] all reduce the aerosol deposition in the lung. Lower density gas such as heliox mixture enable better deposition of the aerosol by decreasing the turbulence of air flow.

Position of the Device

Aerosol delivery to the patient is improved by placement of a nebulizer at a distance of 30 cm from the endotracheal tube[26,29] rather than between the patient wye and the endotracheal tube because the ventilator tubing acts as a spacer for the aerosol to accumulate between breaths.

Suggested Method for Delivery of Drug by Nebulization (Modified from Recommendations by Hess[30])

1. Clear secretions from ET tube.
2. Ensure a high tidal volume to eliminate the deadspace of the tubing.
3. Decrease the inspiratory flow rate so that the inspiratory time is prolonged.
4. Ensure 4-6 ml of volume in nebulizer and place the nebulizer in the inspiratory limb 30 cm from wye connection.
5. Ensure air-flow of 6 L/min to run nebulizer.
6. Nebulize solution only during inspiration.
7. Tap nebulizer intermittently during operation.
8. Disconnect nebulizer from the circuit after use.

Meter Dose Inhaler (MDI)

Only 1 percent of the content of MDI is the active drug. The rest is made up of propellants and preservatives. The amount of the drug delivered by MDI is much smaller than the nebulizer.[23,31] MDI may be used directly on ET tube or through a chamber. A variety of chambers are available for use of MDI during mechanical ventilation. As a rule it is better to use a chamber device than to use MDI directly on the ET tube. The chamber could be collapsible or non-collapsible and be attached to the inspiratory limb of the ventilator circuit.[23] It is preferable to use a collapsible chamber that does not have to be disconnected from the circuit between uses. It is important that the actuation of the MDI is synchronized with the inspiratory time. An aerosol cloud enhancer spacer directs the fumes away from the patient into the spacer.[32,33] The drug then gets carried to the patient during the inspiratory flow. Thus this method of delivery is the most efficient.

Suggested Method of Aerosol Delivery by MDI (Modified from Recommendations by Hess[30])

1. Clear secretions from ET tube.
2. Ensure a high tidal volume to eliminate the deadspace of the tubing.
3. Decrease the inspiratory flow rate such that the inspiratory time is prolonged.
4. Place the acturator- spacer device in the inspiratory limb of ventilator.
5. Shake the MDI and place on the spacer.
6. Discharge MDI at the onset of inspiration.
7. Repeat 20 to 30 seconds later.

Several studies have compared the efficacy of nebulizer and MDI.[26,28] The properly executed MDI may be better than nebulizer. The bio-availability is very poor when one uses the right angle MDI port and hence should not be used to deliver bronchodilator in mechanically ventilated patients.

Of all the medicines used, bronchodilators are the ones that are most commonly delivered as an aerosol. Bronchodilators are used in an asthmatic. In order to reduce air trapping the ventilatory parameters one uses is almost exactly the opposite to the parameters that one has to use for optimization of aerosol delivery. Furthermore humidification is not possible while using aerosol. All this makes it difficult, wasteful and even harmful to use continuous aerosol therapy while on ventilator.

Mucolytics

There are no randomized control trials, in fact any trials at all in the usage of mucolytics (to my knowledge). However, there have been case reports in the use of N-acetylcystine and DNase in life-threatening situations of mucous plugs.[11,23] N-acetylcystine works by breaking the disulphide bonds in the mucus and hence making it less viscid and easier to suction. N-acetylcystine installation has been associated with mucospasm, which can be overcome by using β_2 agonist nebulization. Although DNase is used in patients with cystic fibrosis, it is not routinely used for removing secretions. Its use has been described in neonates and asthmatics with life-threatening mucous plugs. It is expensive and not available in India.

Endotracheal Suctioning

Suctioning can be done using the closed or open suctioning system. In closed suction system the suction catheter is encased in a plastic sleeve and is a part of the ventilatory tubing. The advantage of the closed suctioning system is that cost of disposable is reduced; intuitively the risk of infection has to be less (although there is no proof). The peep effect is not lost while suctioning and hence the risk of hypoxemia in patients with reduced FRC is less.[25] Its disadvantage is that resistance can be increased and it decreases the pulmonary bio-availability of β_2 agonist when used in asthmatics. In order to decrease the viscidity of secretion when not contraindicated, we increase the fluid administration to the patient, i.e. hyper hydrate the patient. In some institutions normal saline installation into the ET tube is routinely practiced. We use it only when the secretions are viscid and copious. While suctioning it is important to remember that mucosal injury can occur. Hence gentle suctioning taking care to not push the catheter up to the carina is a must.

Personally in our ICU we use the open system except in ARDS. In patients with pulmonary hypertension and elevated intracranial pressure, sedation prior to suctioning is a must[34] as significant elevations of pressures and deterioration of hemodynamic parameters can occur.

Eye Care

A ventilated patient is often heavily sedated and may be even paralyzed. This predisposes the individual to exposure keratitis, corneal ulceration and infection. Along with passive closure of the eyelid, using lubricants at scheduled intervals has been shown to provide protection from above mentioned problems. The exact lubricant and the number of times to use it have not been established. We use artificial tears every two hours and if we use an oily lubricant apply it four times a day.

In conclusion, except for a few practices that we use in day to day in the ICU, most methods are not proven to be effective. We should not let our practices be guided by hear say and should practice evidence based medicine as often as possible.

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CHAPTER

Weaning from Mechanical Ventilation

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For many patients, once the need for mechanical ventilation no longer exists, the procedure can be discontinued very rapidly. This includes post-operative ventilatory support for recovery from surgery and anesthesia or uncomplicated drug overdose.

For many others this is often a lengthy complicated process called weaning.

Weaning implies that the need for support still exists and that the patient is ventilator dependent. It is a gradual process that is begun only after there is evidence that the problem leading to the need for mechanical ventilation has resolved.

There are many guidelines and evidence based reports on weaning in adults, however specific criteria based on evidence are not yet established in children.[1-8] Many of the following recommendations or suggestions are based on cumulative data obtained from adults and children.

Pathophysiology of Ventilator Dependence

Patients require mechanical ventilatory support when the ventilatory and/or gas exchange capabilities of their respiratory system fail. This failure could be due to processes within the lung or other systems like the central nervous system (CNS) or cardiovascular system.

The term "ventilator dependent" is usually reserved for patients with a need for mechanical ventilation beyond 24 h or by the fact that they have failed to respond during discontinuation attempts (Table 39.1).

Under these circumstances, the clinical focus should be not only on ventilator management but also should include a search for all of the possible reasons (especially potentially reversible ones) that may explain the ventilator dependency.

Recommendation 1: In patients requiring mechanical ventilation for > 24 hours, a search for all the causes that may be contributing to ventilator dependence should be undertaken. This is particularly true in the patient who has failed attempts at withdrawing the mechanical ventilator. Reversing all possible ventilatory and nonventilatory issues should be an integral part of the ventilator discontinuation process.

Determinants of Weaning Outcome

Table 39. 1: Causes of ventilator dependency

Causes	*Description*
Neurologic controller	Central drive; peripheral nerves
Respiratory system	Mechanical loads: respiratory system mechanics; imposed loading Ventilatory muscle properties: inherent strength/endurance; metabolic state/nutrients/oxygen delivery and extraction Gas exchange properties: vascular properties and ventilation/perfusion matching
Cardiovascular system	Cardiac tolerance of ventilatory muscle work; peripheral oxygen demands
Psychological issues	

Neurologic Issues[9]

The ventilatory pump controller or respiratory center contained in the brainstem is a rhythm and pattern generator, which receives feedback from cortical, chemoreceptive, and mechanoreceptive sensors. The failure of the central controller can be due to structural (e.g. brainstem strokes or central apneas) or metabolic (e.g. electrolyte disturbances or sedation/narcotic usage) factors. Apnea of prematurity is due to non-maturation of the respiratory center. The failure of the peripheral nerves also can be the result of either structural factors or metabolic/drug factors.

Respiratory System Muscle/Load Interactions[10-13]

Often, patients who exhibit ventilator dependence do so because there appears to be a mismatch between the performance capacity of the ventilatory pump and the load placed on it (i.e. the capacity/load imbalance hypothesis). Ventilatory pump performance may be impaired in ventilator-dependent patients because ventilatory muscles are weak from atrophy and remodeling from inactivity or sometimes overuse. Drugs (e.g. neuromuscular blockers, aminoglycosides, and corticosteroids) also can contribute to myopathy. Finally, dynamic hyperinflation can put ventilatory muscles in a mechanically disadvantageous position. Ventilatory muscle fatigue also could contribute to poor muscle performance.

The load on the ventilatory muscles is a function of ventilation demands and respiratory system mechanics (i.e. primarily compliance and resistance). Ventilation demands can increase as a consequence of increased oxygen demands in patients with sepsis and serious infections or increased dead space in patients with asthma. Compliance worsening can be a consequence of lung edema, infection, inflammation, or fibrosis and of chest wall abnormalities such as edema or even surgical dressings. Worsening resistance can be a consequence of bronchoconstriction and airway inflammation. Additional load also can be imposed by narrow endotracheal tubes and by poorly responsive ventilator demand valves.

Patients who go on to fail to respond to ventilator withdrawal attempts because of a capacity/load imbalance tend to display rapid, shallow breathing patterns.

This pattern is advantageous from an energetics perspective, but it is also associated with increased dead space and wasted ventilation, and hence with impaired CO_2 elimination.

Metabolic Factors and Ventilatory Muscle Function[14-21]

Nutrition, electrolytes, hormones, and oxygen transport are all metabolic factors that can affect ventilatory muscle function. Inadequate nutrition leads to protein catabolism and a loss of muscle performance. The normal hypoxic ventilatory response and the hypercapnic ventilatory response have been shown to deteriorate under conditions of semi-starvation. Also, overfeeding can impair the ventilator withdrawal process by leading to excess CO_2 production, which can further increase the ventilation loads on ventilatory muscles. Phosphate deficiency has been associated with respiratory muscle weakness and ventilator withdrawal failure. Magnesium deficiency also has been reported to be associated with muscle weakness, and bicarbonate excretion from inappropriate overventilation (often occurring in BPD (bronchopulmonary dysplasia) patients with chronic baseline hypercapnia) can impair ventilator withdrawal efforts as the patient has a diminished capacity to compensate for hypercapnia.

Severe hypothyroidism and myxedema directly impair diaphragmatic function and blunt ventilatory responses to hypercapnia and hypoxia. Other hormonal factors that are important for optimal muscle function include insulin/glucagon and adrenal corticosteroids.

Gas Exchange Factors

Gas exchange abnormalities can develop during ventilatory support reductions since various lung diseases produce ventilation perfusion imbalances and shunts.

Cardiovascular Factors

Suggested mechanisms include the following:

1. Increased metabolic demands, and hence circulatory demands, that are associated with the

transition from mechanical ventilation to spontaneous breathing in patients with limited cardiac reserve;
2. Increases in venous return as the contracting diaphragm displaces blood from the abdomen to the thorax; and
3. The increased left ventricular afterload that is imposed by negative pleural pressure swings.

Psychosocial Factors

Psychological factors may be among the most important non-respiratory factors leading to ventilator dependence. Fear of the loss of an apparent life support system as well as social/familial /economic issues, particularly in our setup all may play a role.

Stress can be minimized by frequent communication among the staff, the patient, and the patient's family. Environmental stimulation using television, radio, or books also appears to improve psychological functioning. Ambulation (though impractical at times) using a portable ventilator (or bagging) has been shown to benefit attitudes and outlooks in long-term ventilator-dependent patients.

Criteria to Assess Ventilator Dependence[5-7, 22-24]

The process of discontinuing mechanical ventilatory support begins with a recognition of adequate recovery from acute respiratory failure.

Thereafter, careful clinical assessments are required to determine the patient's readiness for subsequent discontinuation of ventilatory support and, ultimately, extubation.

To facilitate this process, investigators have focused on identifying objective criteria to determine the answers to the following questions:

When can efforts to discontinue ventilation be initiated? What assessment strategies will best identify the patient who is ready for ventilator discontinuation? When should extubation be carried out, and how can extubation outcome best be predicted?

Evidence to answer these questions comes largely from observational studies in which a certain parameter (or set of parameters) is compared in a group of patients who either successfully or unsuccessfully have been removed from the ventilator. The general goal of these studies is to find "predictors" of outcome. Evaluating the results from these types of studies can be difficult for several reasons.

First, the "aggressiveness" of the clinician/investigator's weaning and discontinuation philosophy needs to be understood, as it will affect the performance of a given predictor. Second, a number of methodological problems exist with most of these observational studies. For instance, patients are recruited into these studies because investigators believe that there is some reasonable chance of success for ventilator discontinuation. These "entry" criteria often include some form of clinical judgment or intuition, making results from one study difficult to compare to another. Third, assessed outcomes differ from study to study. Some investigators have examined successful tolerance of a spontaneous breathing trial (SBT), others have used permanent discontinuation of the ventilator, and others have combined successful discontinuation and extubation. Based on these (mostly adult) studies, the following recommendations are suggested:

Recommendation 2: Patients receiving mechanical ventilation for respiratory failure should undergo a formal assessment of discontinuation potential if the following criteria are satisfied:

1. Evidence for some/all reversal of the underlying cause for respiratory failure;
2. Adequate oxygenation (e.g., PaO_2 /FiO_2 ratio > 150 to 200; requiring positive end-expiratory pressure [PEEP] $\leq$ 5 to 8 cm H_2 O; $FiO_2 \leq 0.4$ to 0.5); and pH (e.g., $\geq$ 7.25);
3. Hemodynamic stability, as defined by the absence of clinically significant hypotension (i.e. a condition requiring no vasopressor therapy or therapy with only low-dose vasopressors such as dopamine or dobutamine, < 5 μg/kg/min); and
4. The capability to initiate an inspiratory effort.

The decision to use these criteria must be individualized. Some patients not satisfying all of the above criteria (e.g. patients with chronic hypoxemia/hypercapnia) may be ready for attempts at the discontinuation of mechanical ventilation. (Table 39.2)

Recommendation 3: Formal discontinuation assessments for patients receiving mechanical ventilation for respiratory failure should be

Table 39.2: Criteria used in weaning/ discontinuation studies[25-29]

Criteria	*Description*
Objective measurements	Adequate oxygenation ($PO_2 \geq 60$ mm Hg on $FIO_2 \leq 0.4$; $PEEP \leq 5 - 10$ cm H_2O; $PO_2/FIO_2 \geq 150 - 300$); Stable cardiovascular system (e.g., HR ≤ 140; stable BP; no (or minimal) pressors) Afebrile (temperature < 38°C) No significant respiratory acidosis Adequate hemoglobin (Hgb ≥ 8–10 g/dl) Adequate mentation (e.g., arousable, GCS ≥ 13, no continuous sedative infusions) Stable metabolic status (acceptable electrolytes)
Subjective clinical assessments	Resolution of disease acute phase; physician believes discontinuation possible; adequate cough

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*Hgb = hemoglobin; HR = heart rate; GCS = Glasgow coma scale

Table 39.3: Criteria used in several large trials to define tolerance of an SBT[25-29]

Criteria	*Description*
Objective measurements indicating tolerance/ success	Gas exchange acceptability ($SpO_2 \geq 85$–90%; $PO_2 \geq 50$–60 mm Hg; pH ≥ 7.32; increase in $PaCO_2 \leq 10$ mm Hg); Hemodynamic stability (HR < 120–140 beats/min; HR not changed > 20%; systolic BP < 180–200 and > 90 mm Hg; BP not changed > 20%, no pressors required) Stable ventilatory pattern (e.g., RR d" 30–35 breaths/min; RR not changed > 50%)
Subjective clinical assessments indicating intolerance/failure	Change in mental status (e.g., somnolence, coma, agitation, anxiety); Onset or worsening of discomfort Diaphoresis Signs of increased work of breathing (use of accessory respiratory muscles, and thoracoabdominal paradox)

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*HR = heart rate; SpO_2 = hemoglobin oxygen saturation

performed during spontaneous breathing rather than while the patient is still receiving substantial ventilatory support. An initial brief period of spontaneous breathing can be used to assess the capability of continuing onto a formal SBT. (Table 39.3)

The criteria with which to assess patient tolerance during SBTs are the respiratory pattern, the adequacy of gas exchange, hemodynamic stability, and subjective comfort. The tolerance of SBTs lasting 30 to 120 min should prompt consideration for permanent ventilator discontinuation.

Recommendation 4: **The removal of the artificial airway from a patient who has successfully been discontinued from ventilatory support should be based on assessments of airway patency and the ability of the patient to protect the airway.**

Extubation failure can occur for reasons distinct from those that cause discontinuation failure. Examples include upper airway obstruction or the inability to protect the airway and to clear secretions. The risk of postextubation upper airway obstruction increases with the duration of mechanical ventilation, female gender (in adults, not studied in children), trauma, size of ET(endotracheal) tube, presence/absence of cuff and repeated or traumatic intubation. The capacity to protect the airway and to expel secretions with an effective cough is vital for extubation success. Airway assessments generally include noting the quality of cough with airway suctioning, the absence of "excessive" secretions, or the frequency of airway suctioning (e.g. every 2 hours or more).

Managing the Patient Who Has Failed an SBT

Recommendation 5: Patients receiving mechanical ventilation for respiratory failure who fail an SBT should have the cause for the failed SBT determined. Once reversible causes for failure are corrected, and if the patient still meets the criteria, subsequent SBTs should be performed every 24 h.

Recommendation 6: Patients receiving mechanical ventilation for respiratory failure who fail an SBT should receive a stable, nonfatiguing, comfortable form of ventilatory support.There are a number of ventilator modes that can provide substantial ventilatory support as well as the means to reduce partial ventilatory support in patients who have failed an SBT (Table 39.4). A key question, however, is whether attempts at gradually lowering the level of support (weaning) offer advantages over a more stable, unchanging level of support between SBTs. The arguments for using gradual reductions are:

1. That muscle conditioning might occur if ventilatory loads are placed on the patient's muscles and
2. That the transition to extubation or to an SBT might be easier from a low level of support than from a high level of support. Data supporting either of these claims, however, are few. However, maintaining a stable level of support between SBTs reduces the risk of precipitating ventilatory muscle overload from overly aggressive support reduction. It also offers a significant resource consumption advantage in that it requires far less practitioner time. It has been demonstrated that the daily SBT with stable support between tests permitted the most rapid discontinuation. What has not been addressed, however, is whether gradual support reductions coupled with daily SBTs offer any advantages.

Table 39.4: Modes of partial ventilator support[30-38]

Mode	Patient work adjusted by
SIMV	Number of machine breaths supplied (i.e., the fewer the number of machine breaths, the more spontaneous breaths are required)
PSV	Level of inspiratory pressure assistance with spontaneous efforts
SIMV + PSV	Combining the adjustments of SIMV and PSV
VS	PSV with a "guaranteed" minimal tidal volume (PSV level adjusts automatically according to clinician tidal volume setting)
VAPS(PA)	PSV with "guaranteed" minimal VT (additional flow is supplied at end inspiration if necessary to provide clinician VT setting)
MMV	SIMV with a "guaranteed" $\dot{V}E$ (machine breath rate automatically adjusts according to clinician $\dot{V}E$ setting)
APRV	Pressure difference between inflation and release (ie, the less the pressure difference, the more spontaneous breaths are required)

SIMV = synchronized intermittent mandatory ventilation; PSV = pressure support ventilation; VS = volume support; VAPS(PA) = volume assured pressure support (pressure augmentation); MMV = mandatory minute ventilation; APRV = airway pressure release ventilation

Procedure of Weaning from Mechanical Ventilation (Flow chart 39.1)

Process of weaning begins at the time of initiation of ventilation (i.e. minimal ventilatory settings to keep blood gases and clinical parameters within acceptable limits although these settings will be very high).

If such procedure is followed then ventilatory settings would be reduced once the primary pathology/condition that led to ventilation is improving.

How do we know if the Condition is improving?:

- Improving general condition, fever etc.
- Decreasing FiO_2 requirement
- Improving breath sounds
- Decreasing endotracheal secretions
- Improving chest X-rays
- Decreased chest tube drainage,bleeding/air bubbles(as the case may be)
- Improved fluid and electrolyte status(no overload or dyselectrolytemia)
- Improving hemodynamic status
- Improving neurological status,muscle power, airway reflexes/control.

Described weaning criteria such as maximal negative inspiratory force, vital capacity measurement are usually impractical.

In pediatrics and neonatal age group weaning criteria are generally clinical. Ventilatory support in general should be weaned in small percentages (including rates, pressures, volumes and inspired oxygen determining the overall ventilatory support)

Weaning Modes

Three commonly used methodologies include:

1. *T-piece weaning:*[30-34] Patient is made to breathe spontaneously off the ventilator via a T-piece through which O_2 is administered, for increasing intervals of time as tolerated and extubated when criteria for extubation are met.

Advantages–Simple, no "technical expertise" needed, improves muscle recruitment and endurance.

Disadvantages–In small children, the resistance offered by the tube and circuit limit use of this mode. Close monitoring of gas exchange and muscle fatigue is needed, as the muscle training is "abrupt". Diaphragm-intercostal dysynchrony is sometimes seen, again especially in small children.

2. *Intermittent mandatory ventilation*
3. *Pressure support ventilation*

Intermittent mandatory ventilation(IMV): **IMV** with continuous flow ("conventional" weaning). Popularized in neonatal intensive care units (NICUs). Ventilator rate is gradually decreased allowing baby's own respiratory rate to take over. Baby is weaned to minimal rates (6-8), put on CPAP (continuous positive end expiratory pressure) briefly and extubated.

Advantage–Simple, lot of experience and data prove efficacy, less technical know-how. Avoidance of paralysis/sedation, respiratory alkalosis, muscle atrophy.

Disadvantage–Muscle training not optimal, not suitable in older children, requires a continuous flow circuit. Asynchronised, so breath stacking possible.

SIMV

Sychronized mode, prevents breath stacking/ barotraumas. Pre-set rate and volume delivered to patient, however breaths are synchronized with patient's spontaneous efforts by a servo-controlled mechanism. There is a window period around each breath which the ventilator uses for "looking for" a spontaneous breath – the SIMV window, after which the ventilator breath is delivered. During weaning, the set SIMV rate is gradually reduced as patient's spontaneous breaths become adequate. Otherwise similar to IMV. Does not need continuous flow. Servo controlled.

Pressure Support (PS)[35-38]

This is an assist mode, pressure or flow triggered, pressure limited, flow-cycled method. Inspiration ends when a predetermined percentage (usually 25%) of the patients peak inspiratory flow is reached. Patient controls inspiratory flow, time, frequency.

There are three forms of PS ventilation

(a) *PSmax*–as a stand alone form of ventilation. Uses high levels initially depending on the patients tidal volume and compliance, which is then gradually weaned.
(b) *at low levels with SIMV,*
(c) *at low levels with PEEP/CPAP* to overcome resistance of the system preextubation.

Advantage–Permits patient to acquire larger TV (tidal volume) at same level of effort (as in patients with increased airway pressures, decreased compliance), neuromuscular problems (decreases resistance offered by the system). Decreases work of breathing.

Disadvantage–If used without SIMV, patient has to be breathing spontaneously. Needs back-up expired MV(minute ventilation) alarms. Servo controlled, so equipment complicated/expensive.

SIMV with PS–Seems to be ideal for post-neonatal to older children. This mode combines advantages of mandatory synchronized breaths with gradually increasing assisted breaths. Traditionally the mandatory breaths have a preset TV (SIMV with PS, volume control). In the newer servo ventilators the mandatory breaths could also be preset pressure controlled (SIMV with PS, pressure control). This mode is of course dependent on the efficacy of the microchip processor.

Volume Assured Pressure Support (VAPS)

Newer mode, the flow triggered pressure supported breaths also guarantee a minimum preset MV (minute ventilation), thus improving the work of breathing further.

CPAP–Weaning mode pre-extubation. It is often used to overcome resistance of tubing on spontaneous breathing. This mode should not be used for a prolonged period of time as it can lead to muscle fatigue. This mode can also be used with PS.

Goals of Mechanical Ventilation during Weaning

Optimization of ventilatory muscle function. Weaning returns the breathing loads to the patient's ventilatory muscles. The idea is to reduce loads to tolerable levels, and the muscles should have adequate strength and endurance. There is a fine balance between need for ventilation which is imposed by the demands resulting from disease and spontaneous ventilation.

Demands could be in the form of:

1. Pressure loads from decreased lung compliance or increased airway resistance, and
2. Ventilatory loads from increased need for alveolar ventilation or increased dead space.

These demands need to be balanced by the patient's ventilatory capabilities—normal neural drive and adequate muscle function, i.e. strength and endurance. Impaired muscle function may result from residual muscle fatigue, malnutrition and direct effects of the primary disease.

Patient-ventilator Synchrony

Un-coordinated ventilatory pattern increases O_2 consumption and CO_2 production, necessitating a higher minute ventilation. This dysynchrony can lead to an erroneous overuse of sedation. Therefore a pattern that is synchronized with the patient's mechanoreceptors and inspiratory flow demands is desirable. Apart from ventilatory parameters, the high-pressure loads imposed by ventilatory circuits, endotracheal tubes and demand valves.

Pre-requisites to Weaning

Clinical Lab "Technical indices"
Respiratory Systemic
Neuro. Muscle Nutrition Psychological

Respiratory: WOB – RR, retractions, accessory muscles use, sensorium.

Laboratory:

pO_2>60 on FiO_2<0.4,
A-a gradient <350 on FiO_2 of 1.0,
pO_2/FiO_2 >200

"Technical indices": (Not well established in children):

1 Crying vital capacity(VC) > 15 ml/kg,
2 MIF(maximal inspiratory force) > 45,
3 Qs/Qt <20%,
4 Normal oxygenation and CO_2 elimination on minimal PPV (SIMV <4/m, PEEP/CPAP <5) with FiO_2<0.4 predict successful weaning and extubation in majority of patients.

Ventilatory pump indices in older children and adults:

1 VC > 10-15 ml/kg,
2 MIF(maximal inspiratory force) > 30,
3 MV(minute ventilation) <10 L/m,
4 MVV(maximal voluntary ventilation) > twice resting MV,
5 Thoracic compliance >25,
6 Airway occlusion pressure (P0.1) <6,
7 RR(respiratory rate) <25,
8 TV (tidal volume)>300.

Weaning Methodology

There are no set protocols supported by any pediatric studies.

A suggested practical protocol followed at authors institution is as follows:

When FiO_2 requirement is down to 0.4 or lower, improvement in secretions, and chest x rays, improving clinical condition ,muscle relaxant drip(if used) is stopped and sedation can be slowly weaned.

One should change control mode (or PRVC) to SIMV mode with pressure support. If already on SIMV mode with pressure support, then SIMV rate can be reduced by 20 percent.

Pressure support can be set at 10-15 cm above PEEP so that the spontaneous breaths can be adequately supported.

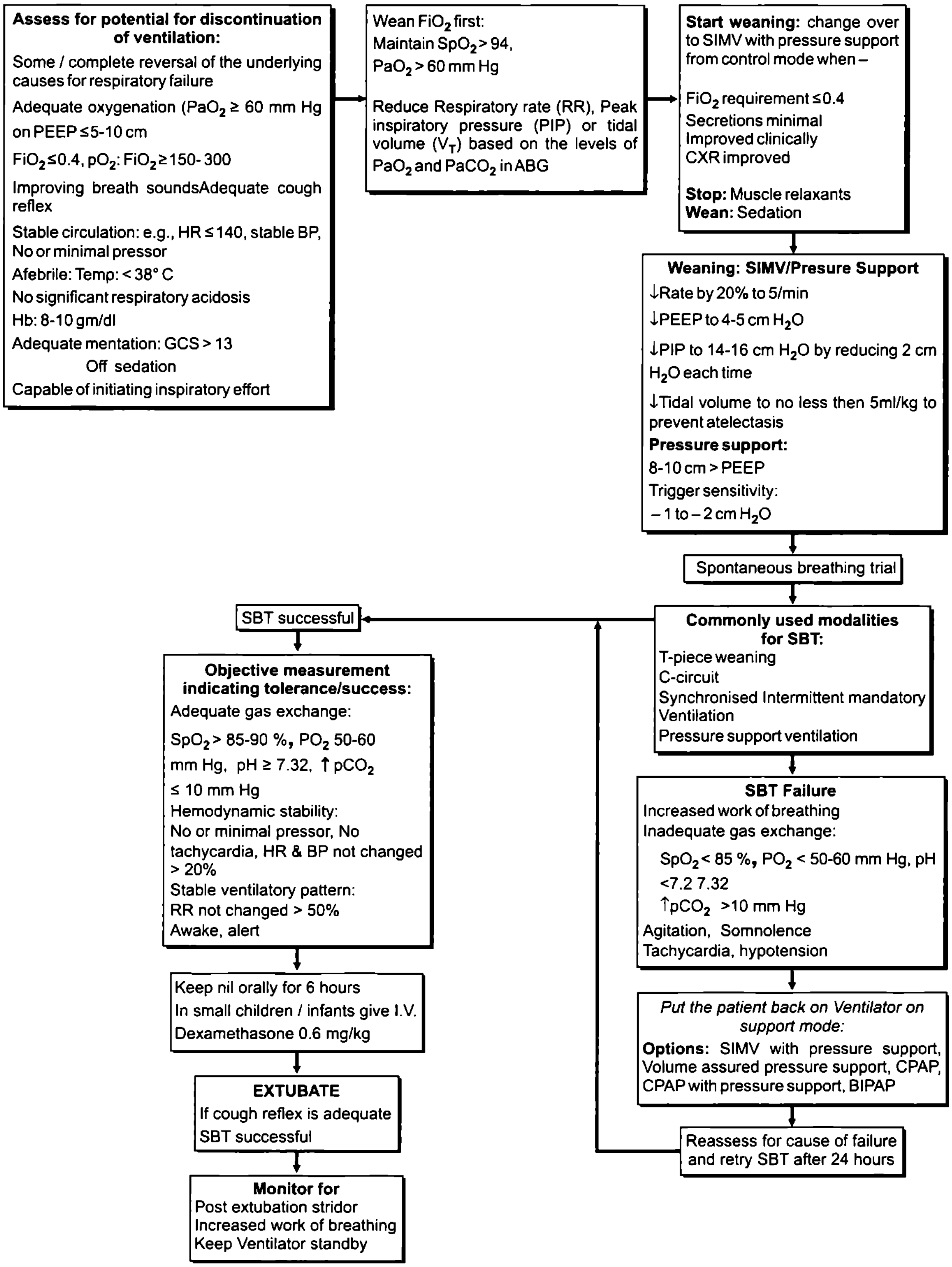
Trigger sensitivity should be 0 to negative one, so that the patient can easily generate a negative pressure to trigger(initiate) the ventilator breath or flow.

Following weaning guidelines can be followed:

1. *Decrease FiO_2 to keep SpO_2>94*
2. *Decrease the PEEP to 4-5 gradually by decrements of 1-2 cm H_2O*
3. *Decrease the SIMV rate to 5 (by 3-4 breaths/min)*
4. *Decrease the PIP (to 20 cm H_2O, by reducing 2 cm H_2O each time/Tidal volume, to no less than 5 ml/kg to prevent atelectasis (usually guided by blood gases)*
5. *Ventilator (SIMV) rate and PIP (or tidal volume) can be changed alternately.*

If at any point patients oxygen requirement increases greater than 0.6, or spontaneous ventilation is fast or distressed with accessory

Flow chart 39.1: Weaning from mechanical ventilation


Assess for potential for discontinuation of ventilation:
Some / complete reversal of the underlying causes for respiratory failure
Adequate oxygenation ($PaO_2 \geq 60$ mm Hg on PEEP ≤5-10 cm
$FiO_2 \leq 0.4$, pO_2: $FiO_2 \geq 150$-300
Improving breath soundsAdequate cough reflex
Stable circulation: e.g., HR ≤ 140, stable BP, No or minimal pressor
Afebrile: Temp: < 38° C
No significant respiratory acidosis
Hb: 8-10 gm/dl
Adequate mentation: GCS > 13
Off sedation
Capable of initiating inspiratory effort
Wean FiO_2 first:
Maintain $SpO_2 > 94$,
$PaO_2 > 60$ mm Hg
Reduce Respiratory rate (RR), Peak inspiratory pressure (PIP) or tidal volume (V_T) based on the levels of PaO_2 and $PaCO_2$ in ABG
Start weaning: change over to SIMV with pressure support from control mode when –
FiO_2 requirement ≤0.4
Secretions minimal
Improved clinically
CXR improved
Stop: Muscle relaxants
Wean: Sedation
Weaning: SIMV/Presure Support
↓Rate by 20% to 5/min
↓PEEP to 4-5 cm H_2O
↓PIP to 14-16 cm H_2O by reducing 2 cm H_2O each time
↓Tidal volume to no less then 5ml/kg to prevent atelectasis
Pressure support:
8-10 cm > PEEP
Trigger sensitivity:
– 1 to – 2 cm H_2O
Spontaneous breathing trial
Commonly used modalities for SBT:
T-piece weaning
C-circuit
Synchronised Intermittent mandatory Ventilation
Pressure support ventilation
SBT successful
Objective measurement indicating tolerance/success:
Adequate gas exchange:
$SpO_2 > 85$-90 %, PO_2 50-60 mm Hg, pH ≥ 7.32, ↑ pCO_2 ≤ 10 mm Hg
Hemodynamic stability:
No or minimal pressor, No tachycardia, HR & BP not changed > 20%
Stable ventilatory pattern:
RR not changed > 50%
Awake, alert
Keep nil orally for 6 hours
In small children / infants give I.V. Dexamethasone 0.6 mg/kg
EXTUBATE
If cough reflex is adequate
SBT successful
Monitor for
Post extubation stridor
Increased work of breathing
Keep Ventilator standby
SBT Failure
Increased work of breathing
Inadequate gas exchange:
$SpO_2 < 85$ %, $PO_2 < 50$-60 mm Hg, pH <7.2 7.32
↑pCO_2 >10 mm Hg
Agitation, Somnolence
Tachycardia, hypotension
Put the patient back on Ventilator on support mode:
Options: SIMV with pressure support, Volume assured pressure support, CPAP, CPAP with pressure support, BIPAP
Reassess for cause of failure and retry SBT after 24 hours

muscle use (increased work of breathing), patient gets lethargic, hypercarbia on blood gas, weaning process should be paused and the support level increased.

Patient may not be ready.

Goal is to decrease what the ventilator does and see if the patient can make up the difference without desaturations/hypercarbia/significant tachypnea and respiratory distress (For example, If patients SIMV was reduced from 20/min to 15/min and the patients spontaneous rate is increased from *25 to 50, this patient may need more time on the* ventilator).

EXTUBATION

Most patients can be weaned to SIMV of 5 and extubated,some will need pressure support 5-10 above PEEP with CPAP, while others may need CPAP 5 cm H_2O before extubation,with or without spontaneous breathing trials(SBT) with T piece. SBT[39] with C circuit can be given for short periods of time (15 min) to assess the patient effort before extubation.

Extubation can Generally be Performed when Following Criteria are met

1. Control of airway reflexes, minimal secretions
2. Patent upper airway (air leak around tube?)
3. Good breath sounds
4. Minimal oxygen requirement <0.3 with SpO_2 >94
5. Minimal rate 5/min
6. Minimal pressure support (5-10 above PEEP)
7. "Awake " patient

Usually if patient can be well for 24 hours after extubation with residual distress settling down as well as no significant increase in oxygen requirement, it is considered a success, and one may communicate with the family accordingly.

Common Causes of Extubation Failure:

Airway issues
Secretions with weak cough
Stridor due to edema, inflammation
Bronchospasm
Atelectasis or significant residual lung disease
Too much sedation or neurological reason for being comatose
Residual paralysis due to muscle relaxation
Muscle weakness
Hemodynamic instability, requirement for significant inotropic support
Fluid overload/pulmonary edema
Electrolyte abnormalities such as
Low potassium, low sodium. abnormal calcium, magnesium, phosphorus

DONT'S

Do not wean pressure or volume parameters if the FiO_2 is 1.

Don't keep PEEP to high level (7 or 9cm H_2O, remember to wean it !) if the FiO_2 is already down to 30.

Summary

General principles of weaning:

1. Weaning should be initiated only after the primary disease/alteration in physiologic status which necessitated ventilation has been reversed.
2. Weaning modes which permit the patient's respiratory system to take over are preferred to abrupt withdrawal techniques in children.
3. Gradual weaning permits muscle strengthening and decreases fatigability.
4. Careful monitoring of patient's clinical and oxygenation/ventilation status essential.
5. Triggering is the term used to describe the process by which the patient initiates enough negative inspiratory force to overcome resistance imposed by the tube/circuit and an additional preset resistance. Triggering is used in patient assist modes of weaning including pressure support modes. Triggering can be pressure or flow triggered.
6. There is no ideal weaning mode. Like all forms of ventilatory therapy, weaning is a learnt art rather than a science. One should get comfortable with a few modes and use it judiciously rather than experimenting with all available newer modes.

Conclusion

Weaning is an art. It needs to be clinically gauged and GRADUAL. Most children with short term ventilation can be weaned with or without a set protocol.

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CHAPTER

40

Complications of Mechanical Ventilation

Praveen Khilnani

Pediatric intensivist needs to be aggressive in use of mechanical ventilation. However, it is recommended to be twice as aggressive in weaning the ventilatory support off when the condition for which it was originally initiated is better. Nevertheless, for the time mechanical ventilation is required, it is not free of adverse effects. Following discussion deals with various adverse effects that are associated with mechanical ventilation in a critically ill child.

Numerous complications may contribute to patient morbidity and mortality.

1. Related to increased airway pressures and lung volume.
   - *Barotrauma/Volutrama:* Pulmonary interstitial emphysema, pneumothorax, pneumopericardium, pneumoperitonium, subcutaneous emphysema.
   - Decreased cardiac filling and poor perfusion
   - Other organ dysfunction; Renal, hepatic, CNS
   - Pulmonary parenchymal damage
   - Adverse effects on gas exchange
   - Increased extravascular lung water.
2. Related to endotracheal/tracheostomy tube
   - Tracheal mucosal swelling, ulceration or damage
   - Sinusitis/middle ear infection (nasal ET tubes)
   - Laryngeal edema, subglottic stenosis
   - Granuloma formation leading to airway obstruction.
3. Nosocomial infections
   - Ventilator associated pneumonias
   - Sepsis.
4. Pulmonary circulation
   - Increased pulmonary vascular resistance
   - Compression of alveolar vessels.
5. Mechanical operational problems
   - Mechanical ventilator/compressor failure Alarm failure
   - Inadequate humidification.
6. Other systems
   - Decreased hepatic blood flow.
   - Decreased cerebral venous drainage.

Mechanical ventilation has diverse effects; some beneficial and others adverse. Beneficial and adverse effects can occur simultaneously. The beneficial effects in the lung are related to improvements in pulmonary mechanics, gas exchange, and hemodynamics.

Adverse effects are mainly related to (i) consequences of positive intrathoracic pressure, and (ii) injury to the airway. These injuries will be discussed in detail.

Airway Injury from Mechanical Ventilation

The presence of an tracheal tube traversing the upper airway can be associated with significant airway injury. Oropharyngeal and nasopharyngeal injuries are rare.

Ulceration of the alae nasi from pressure necrosis may occur following prolonged nasotracheal intubation, particularly if the skin perfusion of the ala nasi is compromised by very tight taping. Similar ulceration may occur at the angles of the mouth from tight taping of tracheal tubes.

Similarly, injuries in the subglottic region may range from minor swelling to major ulceration. Healing of the severe injuries may lead to scarring, granuloma formed with airway obstruction, which may be partial or complex. *The majority of subglottic* *tracheal lesions are due to compression of the tracheal mucosa by the endotracheal cuffs.* High pressure cuffs, cardiovascular instability, upper respiratory tract infection, duration of intubation, and head and neck movement all increase the risk of tracheal injury.

Airway injury can also result from suction catheters. Necrotizing tracheobronchitis is a severe form of airway injury in patients on mechanical ventilation that is characterized by extensive ulceration and mucosal damage. The sequelae of tracheal injuries include tracheal stenosis, tracheomalacia, tracheoesophageal fistula, and tracheoinnominate artery fistula.

Injury to the airway can often be prevented by attention to detail:

- The endotracheal tube should be the proper size with a cuff leak around it at < 20 cm H_2O positive pressure.
- Excessive pressure on the skin should be avoided while taping the endotracheal tube.
- Excessive patient movement should be prevented by adequate sedation and restraints.
- Suctioning should be gentle, preferably with a catheter with multiple side holes.
- Silicon catheters should not be routinely advanced beyond the tip of the endotracheal tube.

Effects on the Lung

Adverse effects of mechanical ventilation on the lung may be due to

1. High airway pressures,
2. Overdistention of the alveoli,
3. Altered mucociliary clearance,
4. Lung water clearance, and
5. Oxygen toxicity.

The adverse effects of positive pressure ventilation may be manifested as:

1. Parenchymal injury,
2. Altered ventilation-perfusion relationship leading to impaired gas exchange, and
3. Increased risk for infection.

Increased airway pressure may cause hyperinflation of alveoli and predispose to alveolar rupture. Hyperinflation may increase alveolar deadspace, impair cardiac filling, and compress alveolar vessels. "Pulmonary barotrauma" is a loose term that encompasses many forms of parenchymal injury. *Volutrauma (injury due to high tidal volume and stretch related injury) is being commonly recognized.* Alveolar rupture from overdistended alveoli is the most common manifestation of pulmonary barotrauma.

Air leak may occur from the lung into the Pleura (pneumothorax), the interstitium (pulmonary interstitial emphysema, PIE), the mediastinum (pneumomediastinum), and the subcutaneous tissue (subcutaneous emphysema).

Even though the term implies high airway pressures as the main mechanism of parenchymal injury, pulmonary barotrauma is often multifactorial. The physiological consequences of extra-alveolar air range from inconsequential to life-threatening.

A pneumothorax may be small and in consequential or may be large and tense. Tension pneumothorax requires immediate evacuation.

PIE may decrease lung compliance and increase pulmonary vascular resistance.

Pneumomediastinum requires careful observation. The natural tendency of pneumomediastinum is to track along fascial planes either cephalad to produce subcutaneous emphysema of caudad to produce pneumoperitoneum or pneumoretroperitoneum.

Pneumomediastinum rarely requires evacuation.

Pneumopedcardium can range from a minimal, inconsequential amount of air to life-threatening cardiac tamponade.

Cardiovascular compromise is an indication of immediate evaculation of pericardial air.

A special form of pulmonary air leak is a bronchopleural fistula, where a fistulous track develops between the bronchus and the pleural space. This results in an almost continuous flow of air from the airway into the pleural space.

The fistulous flow is wasted ventilation and may result in hypercarbia. Attempts to increase minute ventilation by increasing tidal volume may only serve to increase the leak from the fistula. Attempts to decrease airway pressures with conventional ventilation are not possible without compromising gas exchange, high frequency ventilation may be tried.

Prevention of Barotrauma

The principal factors that can be controlled in an effort to minimize barotrauma are airway pressures and lung volumes. As long as acceptable gas exchange is mainstained, every effort must be made to minimize tidal volumes and airway pressures. Hyperinflation must be avoided. When lung disease is severe, hypercarbia may be tolerated (*Permissive hypercapnea*) provided the arterial pH is adequate (> 7.2). Inspired oxygen concentration should be maintained at nontoxic levels usually < 0.5.

Effects on Circulatory System

The cardiovascular effects of positive intrathoracic pressure are complex and depend on the underlying lung disease, uniformity of lung disease, transmission of airway pressure to the pleural space, and lung volume. Coumand was one of the first to demonstrate that positive pressure ventilation decreased cardiac output.

Positive intrathoracic pressure impedes right ventricular filling by decreasing the pressure gradient to venous return. Positive airway pressure also increases pulmonary vascular resistance provided the airway pressure exceeds left atrial or critical closing pressure.

Positive intrathoracic pressure has also been shown to decrease left ventricular afterload. The net effect is a combination of all the effects mentioned above and the reflex cardiovascular adjustments that accompany these changes. *Mechanical ventilation may also decrease urine output, hepatic, portal venous, and mesenteric perfusion.* Many of these effects can be offset by volume loading with fluid boluses.

Nosocomial Pneumonias

Nosocomial pneumonias, sepsis, nosocomial sinusitis can occur with prolonged ventilation. Pseudomonas and gram-negative enteric organisms are commonly colonizing the ventilatory circuit, therefore use of disposable circuits as well as change of circuit (upon visible soiling) may reduce the colonization and chances of nosocomial pneumonias. This issue is discussed in Chapter on Nosocomial Infections.

COMPLICATIONS RELATED TO ADJUNCTIVE THERAPIES

Patients who are mechanically ventilated almost invariable require sedation and analgesia. The physician should be well versed with the adverse effects of the agents used. Most sedative agen result in systemic vasodilatation and depress th cardiovascular system, resulting in hypotension. Th is especially prominent in those who are hypovolem or have an already depressed myocardium.

Since these agents may be used continuously fo prolonged periods, there may be tachyphylaxis requiring escalating doses to provide the same effec In addition, there may also be the development o dependence, which can result in withdrawa symptoms unless the drug is tapered.

Some patients also require neuromuscula blockade while ventilated. Sustained use o neuromuscular blockers (NMB's) may result in prolonged weakness. This problem is commonly associated with the use of some NMB's in conjunction with steroids. NMB's should be used only when absolutely essential and the patient should be monitored adequately (with Train of Four stimulation) to ensure that excessive dosage is avoided. If Train of Four stimulation is not possible then the NMB can be stopped once daily until there is evidence of recovery from blockade, before being reinstituted.

Mechanical Misadventures

Various problems can occur during mechanical ventilation, including ET tube obstruction, ET tube migration, disconnection, unplanned extubation and equipment failure.

Health care providers should be aware of these issues and monitor the patients closely so that such instances can be prevented or minimized.

SUMMARY

Common adverse effects of mechanical ventilation include skin irritation by endotracheal tube tape, tracheal suction injury, airway edema, baro/volutrauma, cardiovascular effects and nosocomial pneumonias.

Most of them can be recognized early, or preferably, can be prevented by attention to detail. Recently permissive hypercapnea and low tidal volume ventilation have been shown to improve outcomes in patients with acute Respiratory Distress syndrome (ARDS) and minimize volutrauma related lung injury. Endotracheal suctioning should be under sterile precautions and gentle at the level above the distal tip of the endotracheal tube. Chronic lung disease, oxygen toxicity and subglottic/tracheal stenosis may still be seen despite all preventive efforts due to critical condition of the child requiring cuffed tube, high airway pressures and high FIO_2.

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CHAPTER

41

Noninvasive Ventilation

Rajiv Uttam, Praveen Khilnani

Intubation and mechanical ventilation are frequently necessary to treat critically ill infant or child who develops hypoxemia and respiratory failure. Placement of an endotracheal tube and initiation of mechanical ventilation predisposes to potential complications, such as nosocomial infection and tracheal injury as well as difficulties with sedation of an intubated child. A significant mortality and morbidity is induced by baro- and volutrauma, as well as by nosocomial pneumonia associated with invasive ventilation by endotracheal tube or tracheotomy. NIV using natural mechanisms of respiratory physiology; it is designed to reduce the lung injury and side effects from mechanical ventilation.

Ventilatory support delivered without establishing an artificial endotracheal airway, is termed non-invasive ventilation.

Traditionally non-invasive ventilation has been administered with the use of devices that apply intermittent negative extrathoracic pressure. The advent of positive pressure ventilation that is delivered through a nasal or face mask has greatly expanded the use of non-invasive ventilation. Such ventilation has a role in the management of acute and chronic respiratory failure in many patients.

Role of Spontaneous Breathing in Respiratory Physiology

During the inspiratory phase of spontaneous breathing, intrathoracic pressure is negative. The action of the diaphragm and airway anatomy favor ventilation to well-perfused dependent zones of the lung, assuming a ventilation perfusion ratio (VA/Qp) of approximately 1 in normal conditions. Positive pressure controlled ventilation or diaphragmatic palsy inversely promotes non-dependent zones ventilation, while dependent (well perfused) zones are less ventilated. V_A/Qp ratio becomes inhomogeneous with improvement in non-dependent zones and venous admixture in dependent zones. This mechanism drives a decrease in arterial oxygenation that can be restored or avoided with NIV.

MECHANISM OF IMPROVEMENT WITH NONINVASIVE VENTILATION

Several theories have been proposed to explain why intermittent NIPPV is effective. One possible explanation is that intermittent rest of clinically fatigued muscles improves respiratory muscle function. During non-invasive ventilation diaphragmatic electromyography activity and respiratory muscle work are reduced. NIPPV also improves lung compliance in patients with neuromuscular or chest wall disease possibility by re-expanding areas of microatelectasis. Another possible explanation is that by preventing nocturnal hypoventilation, nocturnal NIPPV prevents the blunting of the central ventilatory drive that occurs with hypercapnia.

Advantages of NIPPV

Bi-level positive airway pressure (BIPAP) has a low impact on pulmonary circulation, improve oxygenation and recruitment when continuously used. When spontaneous ventilation with or without controlled-ventilation can be maintained, a much lower level of sedation is required. Light sedation has several advantages, reducing interference with hemodynamic functions, avoiding respiratory muscles atrophy, and allowing active mobilization and active cough with a better clearance of secretions. Some studies in adults have shown a decreased incidence of nosocomial pneumonia in NIPPV when compared with all modes of ventilation associated with endotracheal intubation.

Indications for NIPPV

Acute Diseases

- Acute lung injury
- Lung infection
- Acute pulmonary edema
- Bronchiolitis.

Chronic Diseases

- Obstructive pulmonary diseases
- Obstructive sleep apnea
- Cystic fibrosis
- Neuromuscular diseases
- Anterior horn cell disease
- Guillain-Barré syndrome
- Myasthenia gravis
- Phrenic palsy, injury or disease
- Kyphoscoliosis
- Surgery on the right heart
- Total cavopulmonary connection
- Fontan procedure
- Tetralogy of Fallot
- Diaphragmatic palsy.

Non-invasive ventilation can be applied in two ways:

1. *Non-invasive negative pressure ventilation* (NINPV): It supports ventilation by exposing chest wall to subatmospheric pressure inspiration, with expiration occurring as pressure around the chest wall is allowed to return to atmospheric levels. Body ventilators apply negative pressure to the entire body below neck, by using iron lung. Currently less bulky and more portable devices have been designed to apply negative pressure. These ventilators have so many disadvantages such as an awkwardly large size, positioning of the patient, and an increased likelihood of upper airway obstruction, leading to a gradual decline in use of this method of ventilation. The use of NINPV in acute respiratory failure is unclear. However, patients with neuromuscular diseases, chest wall deformity, central hypoventilation or diaphargmatic paralysis often do benefit from negative pressure ventilation.
2. *Non-invasive positive pressure ventilation* (NIPPV):[1,2] Non-invasive positive pressure ventilation refers to delivery of positive pressure ventilation to lungs without an invasive airway. The rationale for use of NIPPV is avoidance of endotracheal intubation and its complications. The use of NIPPV has gained increasingly widespread acceptance, for both acute and chronic respiratory failure after the use of nasal or face mask especially in pediatric patients.[3,7]

Non-invasive positive pressure ventilation[1,4] can be given by:

1. Volume ventilator.
2. Pressure controlled ventilator.
3. Pressure support ventilation.
4. Bilevel positive airway pressure ventilator.
5. Continuous positive airway pressure devices.

Volume Ventilation

Volume cycled non-invasive ventilation in which the ventilator delivers a set tidal volume for each breath can improve outcomes in acute respiratory failure and has been used to manage chronic respiratory failure.

However, patient tolerance is often poor, as inspiratory pressures may be too high, which can be uncomfortable and can cause leaks. In these ventilators tidal volume is fixed, inflation pressure may vary.

Tidal volume can be increased to 20-25 ml/kg as this is an open system, but should always be titrated. The assist control mode ensures that tidal breaths are triggered or improved depending on magnitude of inspiratory effort. These modes are preferred non-invasively in patients with neuromuscular diseases who need high tidal volume for ventilation. Leaks are more common with volume mode.

Pressure Control Ventilation[1,4]

Positive pressure non-invasive ventilation in which the ventilator delivers a set pressure for each breath, is commonly given with bilevel positive airway pressure (BIPAP) ventilators or with standard ventilators that use pressure support or pressure control.

In these modes flow will vary according to patient demands. The ventilator maintains a preset pressure and flow will vary according to resistance. In this mode tidal volume may decrease when there is no spontaneous inspiratory effort or it is just adequate to trigger ventilator. The respiratory rate and I:E ratio can be set on the device.

Pressure Support Ventilation[1,4]

It is the most popular mode used for non-invasive mechanical ventilation. The ventilator is triggered by the patient and when there is fall in inspiratory flow below threshold preset on the ventilator, the ventilator cycles to expiration. Presssure support is commonly given with Bilevel PAP ventilators. Administering ventilation through a nasal or face mask and standard ventilator allows physician to set inspired oxygen concentration, prevent rebreathing of exhaled gas and use the ventilator alarms and monitors. The pressure support mode delivers the flow when ventilator senses a patient initiated breath and terminates the higher pressure when it detects a fall in flow rate below a threshold value or after a prolonged period.[1]

It is usually well tolerated by patients, however, there can be problems if air leak is present. The problem can be tackled by using pressure control ventilation, which sets a fixed inspiratory time and provides a backup rate.

Bilevel Positive Airway Pressure Ventilator (BIPAP)[1,3,20]

Bilevel PAP ventilators provide continuous high flow PAP that cycles between a high positive pressure and a lower positive pressure. These devices are sensitive and can detect inspiratory efforts even in presence of leak in circuit. In spontaneous mode, Bilevel PAP responds to patient's own flow rates and cycles between higher pressure and lower pressure. It is essentially similar to pressure support ventilation in concept.

Continuous Positive Airway Pressure (CPAP)

It is applied when the patient is breathing spontaneously. It can be applied by nasal prongs or nasopharyngeal prongs. Nasal prongs constitute a simple system for application of CPAP. Mouth leak provides pressure pop-off but introduces variation in level of CPAP. This system requires high flow of oxygen. Nasopharyngeal prongs are like endotracheal tube inserted through nose to hypopharynx. The length and diameter of any long prong in CPAP system increases resistance and work of breathing. It is very useful in postoperative high risk patient with severe nonhypercapnic oxygenation failure and avoids reintubation.[5,8]

Practical Applications of Noninvasive Positive Pressure Ventilation (Flow chart 41.1)

Chronic Respiratory Failure

NIPPV is commonly used at night for management of chronic respiratory failure. It has proven to be useful in long-term management of neuromuscular disease.

NIPPV during sleep significantly improves day time arterial blood gases, lung volumes and respiratory muscle strength and reduces the number of admissions of patients with severe kyphoscoliosis.[9]

It can be used as maintenance therapy in patients with intrinsic lung disease and marked hypercapnia. Non-invasive ventilation can be helpful in some patients with intractable dyspnea.

Acute Respiratory Failure

NIPPV is an effective means of treating patients with acute respiratory failure due to variety of causes.

Uncontrolled studies using historical controls and prospective randomized studies have shown consistently good results.[9]

Non-invasive ventilation has been successfully used in patient with cystic fibrosis. In pediatric patients with respiratory insufficiency, but without multiple organ system failure, the use of bilevel positive airway pressure support can decrease the need for placement of an artificial airway.[1,10-12]

Non-invasive ventilation can be effectively used in acute respiratory failure due to pneumonia, exacerbation of reactive airway disease, bronchopulmonary dyspasia, asthma, postoperative hypoventilation with atelectasis, sleep aggravated breathing disorders, patient who are not candidates for intubation.[13-19]

Initiation of Noninvasive Mechanical Ventilation

NIPPV can be given both by conventional ventilators available in pediatric ICU or by specific bilevel positive pressure support ventilation device, which will be discussed here.

Initially, the mask is gently positioned over the nasal bridge with minimal flow. The initial settings are inspiratory positive pressure of 4 to 5 cm of H_2O and expiratory positive pressure 2 to 3 cm of H_2O.

Inspiratory positive airway pressure is followed by expiratory positive airway pressure. As the delivered pressures are increased, the patients breathing pattern is observed for chest excursions and breath sound are auscultated for increase in ventilation. Pressures are adjusted to maximize patient comfort level and stability in pattern of oxygenation. Supplemental oxygen can be given via a connecting tube attached to face or nasal mask.

If oxygenation needs are a major concern expiratory positive airway pressure is optimized. If ventilation is needed to be enhanced as judged by increased $PaCO_2$, the pressure differential between inspiratory positive airway pressure and expiratory positive airway pressure is adjusted because a wider pressure gradient enhances ventilation.

Patient comfort should be always kept in mind and mask should not be too tight to cause discomfort. Small amount of air leak is acceptable. Non-invasive ventilation works best if the patient is relaxed and is less effective if the patient is anxious, uncooperative or fighting with the ventilator. Preparation of patient is critical. In non-emergency situations, the first few sessions can be used simply to fit the mask and familiarize the patient with the apparatus.

Limitations of NIPPV

When NIPPV is applied, patient must be monitored and attention given to their comfort, level of dyspnea, respiratory rate and oxygen saturation. Patients must be watched for signs of ventilator, patient asynchrony, nasal mask intolerance, serious air leaks, gastric distension, drying of the eyes and facial skin breakdown, especially at the bridge of the nose. For a variety and reasons, NIPPV techniques are not always successful. Hemodynamic instability, deteriorating mental status and increasing respiratory rate indicate failure. In general, noninvasive ventilation should not be used in patients who are unable to cooperate or who have impaired consciousness, problems with retained secretions or hemodynamic instability.

Monitoring during NIPPV[1,3,4,20]

Efficacy of NIPPV is determined by observing the effect on heart rate, respiratory rate, oxygen saturation, oxygen requirement and arterial blood gases. Subjective variables include patients work of breathing and dyspnea score. There should be regular monitoring of mask fit, comfort, air leak, secretions and skin necrosis. Proper monitoring is very important for NIPPV to be successful after its application (Figs 41.1A and B).

1. *Patient comfort* The smooth adaptation to the ventilator by the patient is the key to success. If the patient is complaining of discomfort, one should try to make it comfortable either by proper fitting of mask or changing interface. One should not force patient to use device against their will.[1]
2. *Vital signs* Monitoring of vital signs like heart rate, respiratory rate, blood pressure and use of accessary muscle specially sternocleiodomastoid muscle. Dyspnea, mental status, complications like abdominal distension, pressure necrosis and the retention of secretions. Try to get patient to relax as much as explaining him so that he can synchronize well with ventilator and unload his work of breathing.
3. Continuous pulse oximetry.
4. Arterial blood gas.

Blood gas should be done within one hour of initiation of ventilation to adjust ventilatory settings and later at 2 to 6 hour interval.

Patient need not to be sedated. Relief of dyspnea and respiratory distress are achieved but correction of acidosis may be slower. Patients showing improved gas exchange within one hour of initiation of ventilation are less likely to get intubated.

The first 30 minutes of NIPPV are laborious and intensive. Providing reassurance and adequate explanation is very important. Patient or the parent may be instructed to call if the child needs any help, like removal or repositioning of mask, for oral intake or expectoration of secretions.

Figs 41.1A and B: Patient on NIPPV (BIPAP on respironics NIPPV ventilator) *(For color version see Plate 11)*

Indication for early discontinuation of NIPPV:[3]

1. Worsening level of sensorium
2. Extreme distress and anxiety
3. Inability to clear secretions
4. Hemodynamic instability
5. Worsening oxygenation to inability to maintain saturation.
6. Inability to tolerate mask due to discomfort/pain.

Weaning

Once the primary cause has been reversed and patient is better, weaning should be tried. Intermittent weaning can be done by removal of mask initially for few hours and if patient tolerates it well, one can gradually increase the period and then discontinue. Initially weaning should be done during day time and continued during the night for first 1 to 2 days. If patient tolerates it well, NIPPV can be discontinued. ABG must be done to assess success of weaning regularly.

Complications of NIPPV

NIV complications are related to the mode of ventilation.

Collapse of upper airway is the main problem encountered with the *negative-pressure extrathoracic ventilation* and is more frequent with overweight patients. Other complications like pain, esophagitis, rib fractures or pneumothorax are linked to the cuirass itself.

Bruises and Erosions

Problems linked to NIPPV are related to the interface between the patient and the ventilator. Skin bruises on the nasal bridge or the chin or on the flares with nasal canulae can be minimized when the adequate size and type of interface is selected and with placement of comfeel or duoderm between the skin and the interface. Pediatric studies report a complication rate of 7 to 12 percent, mainly facial skin necrosis.

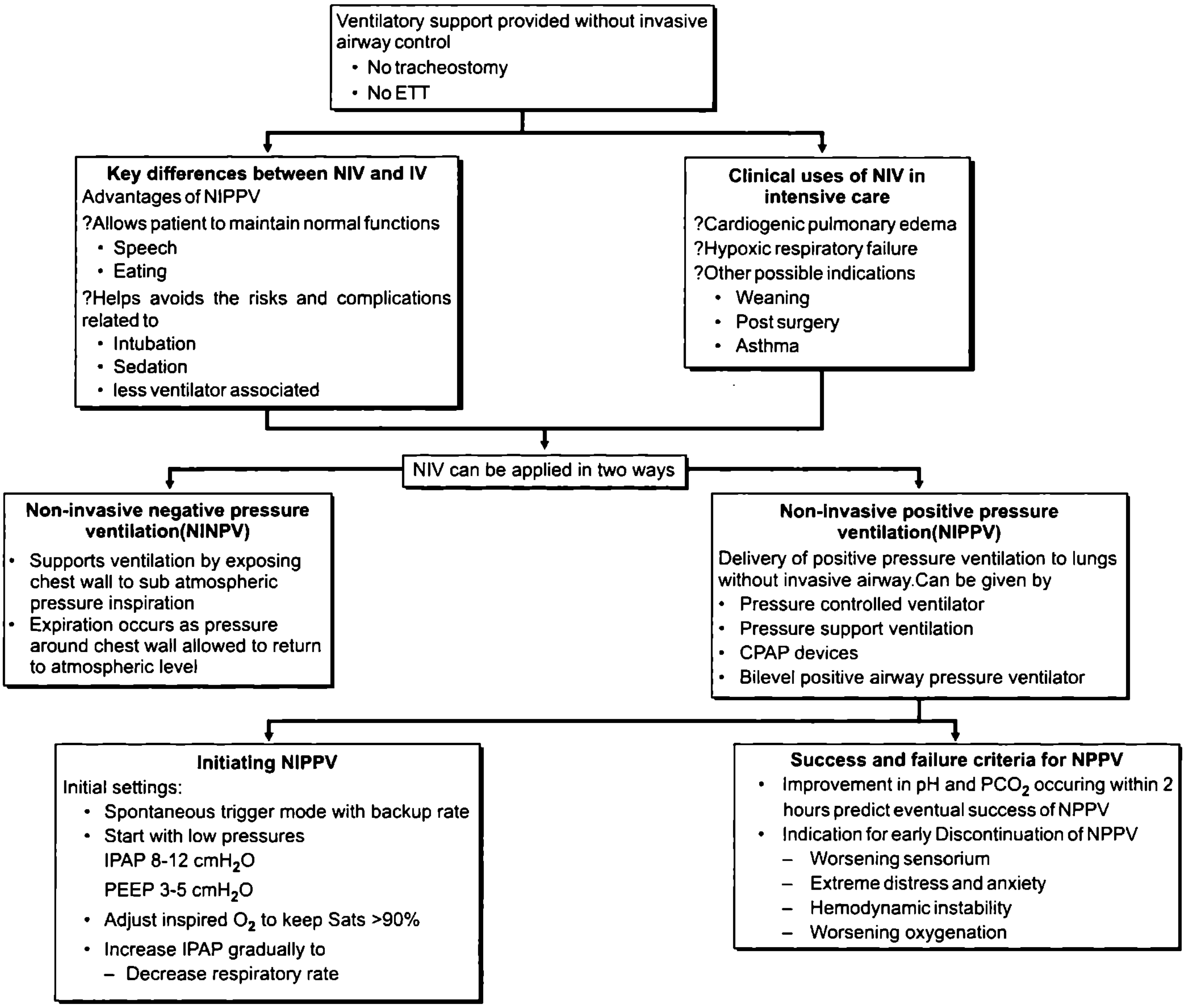
More serious complications like barotrauma or aspiration pneumonia are related to NIV in less than one per cent of patients.[12] Other complications described in children are gastric distention (with IPAP of more than 25 cm H_2O and above the opening pressure of the low esophageal sphincter), non-fitting mask, intolerance and bad adaptation of the child to the interface.

Contraindications to NIPPV include hemodynamic instability, loss of airway protective mechanisms, loss of consciousness, and very thick oral or tracheal secretions.

CONCLUSIONS

NIPPV can be safely administered outside the pediatric ICU or at home if required for long term nocturnal support for sleep related breathing disorders. NIPPV is of potential benefit in acutely critically ill pediatric patients with acute respiratory distress as a means of avoiding intubation. NIPPV should be considered in patients clinically judged to be in early acute respiratory distress and who would otherwise require an artificial airway for respiratory support. NIPPV can result in decrease in heart rate, respiratory rate and dyspnea scores and improvement in gas exchange can occur in patient with underlying neuromuscular diagnosis or patients with chronic lung disease with acute exacerbation. Proper patient selection is essential. Experienced staff must be available and surveillance must be maintained closely to avoid dangerous delays if intubation necessary. Effective NIPPV reduces the duration of ventilatory support and its associated complications. Mortality from acute respiratory failure also may be decreased when endotracheal intubation is avoided. For these reasons pediatric intensivist should become familiar with this modality and consider its implementation for eligible patient group (Flow chart 41.1).

Flow chart 41.1: Noninvasive ventilation



Ventilatory support provided without invasive airway control
- No tracheostomy
- No ETT

Key differences between NIV and IV
Advantages of NIPPV
?Allows patient to maintain normal functions
- Speech
- Eating

?Helps avoids the risks and complications related to
- Intubation
- Sedation
- less ventilator associated

Clinical uses of NIV in intensive care
?Cardiogenic pulmonary edema
?Hypoxic respiratory failure
?Other possible indications
- Weaning
- Post surgery
- Asthma

NIV can be applied in two ways

Non-invasive negative pressure ventilation(NINPV)
- Supports ventilation by exposing chest wall to sub atmospheric pressure inspiration
- Expiration occurs as pressure around chest wall allowed to return to atmospheric level

Non-invasive positive pressure ventilation(NIPPV)
Delivery of positive pressure ventilation to lungs without invasive airway.Can be given by
- Pressure controlled ventilator
- Pressure support ventilation
- CPAP devices
- Bilevel positive airway pressure ventilator

Initiating NIPPV
Initial settings:
- Spontaneous trigger mode with backup rate
- Start with low pressures
  IPAP 8-12 cmH_2O
  PEEP 3-5 cmH_2O
- Adjust inspired O_2 to keep Sats >90%
- Increase IPAP gradually to
  - Decrease respiratory rate

Success and failure criteria for NPPV
- Improvement in pH and PCO_2 occuring within 2 hours predict eventual success of NPPV
- Indication for early Discontinuation of NPPV
  - Worsening sensorium
  - Extreme distress and anxiety
  - Hemodynamic instability
  - Worsening oxygenation

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CHAPTER

High Frequency Ventilation

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Respiratory failure is a final common pathway for many hospitalized patients regardless of etiology. Conventional mechanical ventilation is the mainstay of support for these patients. Support strategies initially utilize minimal ventilator settings to achieve oxygenation and ventilation. As lung pathology evolves, increasing ventilator support may result in additional lung injury referred to as ventilator associated lung injury. When the disease process of the lung progresses and conventional positive pressure ventilator support are being increased, alternative modes of ventilation should be considered to maintain oxygenation and ventilation while preventing further lung injury.

VENTILATOR INDUCED LUNG INJURY

Insults to the lung tissue often result in a heterogeneous pattern of injury represented by areas of inflamed lung and areas of normal lung.[1] When providing positive pressure support to the diseased lung to overcome atelectasis and recruit alveoli, shear stress occurs opening the alveoli of the diseased lung and creating injury to the already compromised area.[2] Simultaneously, areas of normal lung are subjected to positive pressure required for the diseased areas of lung, thereby subjecting the healthy lung to injury. Lung injury from high pressure is referred to as baro-trauma and when it is the result of volume it is referred to as volutrauma. Furthermore, prolonged exposure to $FiO_2 > 0.6$ has been implicated in furthering the inflammatory insult in the lung through oxidative damage via free radicals and absorbtive atelectasis.[2-5] Therefore, the use of positive pressure conventional mechanical ventilation may result in an iatrogenic insult to the already compromised lung referred to as ventilator associated lung injury. The stress on the lung tissue results in release of cytokines and inflammatory mediators, contributing to both local and systemic effects.[6] The local effects increase lung inflammation, worsen capillary leak, and decrease lung compliance. Ultimately, this lung injury will gradually result in escalating ventilator support and this further increases stress to the already compromised lung leading to ARDS. The systemic effects result in diffuse inflammation potentially causing or contributing to multi-organ system failure (MOSF).[7] Therefore, ventilator strategies should be utilized to provide optimal ventilation and perfusion, to minimize positive-pressure related parenchymal damage, and enable highest possible recovery of compromised lung.[8]

PROTECTIVE STRATEGIES OF CONVENTIONAL MECHANICAL VENTILATION

In order to avoid ventilator associated lung injury several protective 'strategies are commonly employed in clinical practice. Avoiding prolonged exposure to oxygen FiO_2 greater than 0.60 to minimize oxygen induced injury to the lung. Whether in volume or pressure support mode one should follow the peak and mean airway pressures to minimize volutrauma and barotrauma. Typically, the peak airway pressures less than 35-40 cm H_2O and peep between 5-15 cm H_2O are both consistent with currently accepted clinical practice.[5,7,9] When support reaches these points ($FiO_2 \geq 0.60$, $PIP \geq 35$, $Paw < 25$ and $PEEP \leq 15$), alternative strategies may be employed to support the respiratory system.

BASIC CONCEPTS OF HFV (HIGH FREQUENCY VENTILATION)

The basic concept of high frequency ventilation is to use smaller than physiologic tidal volumes (tidal volume ≤ dead space) at supra-physiologic rates to support ventilation and oxygenation. The underlying benefit is based on the premise that HFV will result in less barotrauma and volutrauma when compared to prolonged conventional ventilation support at high levels of support. The basic types of HFV are broadly classified and described in the following section.[2,10-13] The actual mechanisms of gas exchange in HFV rely on several mechanisms: principles of direct bulk convection, longitudinal (Taylor) dispersion, Pendeluft, asymmetric velocity profiles, cardiogenic mixing and molecular diffusion.[12]

TYPES OF HIGH FREQUENCY VENTILATION

High Frequency Positive Pressure Ventilation (HFPPV)

Typically capable on most conventional mechanical ventilators with a neonatal setting and low compliance tubing. Oxygen is supplied from a high-pressure gas source. Gas delivery and flow is provided by a pneumatic valve system delivering the oxygenated gas during inspiration. Thereby, inspiration is active and expiration is passive. Typical settings might include; tidal volumes (3-4 ml/kg) or ≤ dead space, rates range between 60 and 150, and inspiratory times are relatively short with I/E ratios of 0.3. Adjustments to normalize blood gases are similar to managing CMV.

High Frequency Jet Ventilation (HFJV) (Fig. 42.1)

Ventilation is delivered by low compliance, low volume tubing and a jet catheter inserted or built into the endotracheal tube which is attached to a special ventilator. The jet catheter is ideally positioned at the end of the endotracheal tube. This catheter creates the driving pressure for ventilation from high-pressure gas source. This gas source creates an airway driving pressure between 0-50 pounds per square inch and is adjusted by a valve. An additional valve creates high frequency sequential interruptions in the driving pressure. This creates small, rapid bursts of positive pressure coming from the jet catheter. The small interruptions are relative drops in airway pressure and allow for passive expiration. Thereby, the driving pressure in the airway is created by rapid burst of airway pressure resulting in active inspiration and expiration is passive. Typical settings often include: tidal volumes are either less than or equal to physiologic dead space (2-5 ml/kg), inspiratory times 10 to 50 per cent of the inspiratory cycle, ventilator rates range between 300-1200. Attachments to the endotracheal tube may be used to maintain PEEP (valve) or provide oxygen reservoir (reservoir bag) in the spontaneously breathing patient.

High Frequency Oscillatory Ventilation (HFOV) (Fig. 42.2)

This type of ventilation features active inspiration as well as active expiration delivered by a special ventilator. Low volume, low compliance tubing is used to deliver support from a special ventilator. Flow is generated from a piston driven acoustic speaker cone, or diaphragm. Movement of this diaphragm creates sinusoidal oscillations in the airway pressure relative to the mean airway pressure. The fluctuations in airway pressure higher than the mean airway pressure create an inspiratory

Fig. 42.1: Bunnell jet ventilator

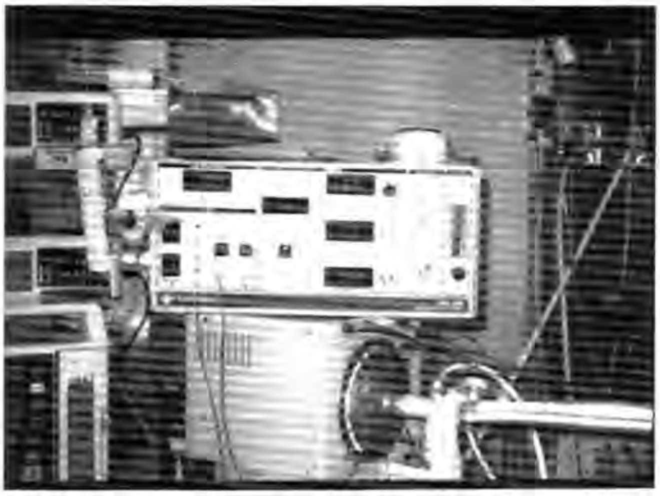

Fig. 42.2: Sensormedics oscillator

force, and pressure less than the mean create a relatively negative or expiratory force. The tidal volumes < dead space are used, typically 1-3 ml/kg. Rates in frequency set between 1 to 60 Hz (60-3600 cycles per minute). In practice, mean airway pressure recruits lung volume, prevents atelectasis and thereby supports oxygenation along with FiO_2. The two main factors determining ventilation are Hz and delta P. Delta P is the pressure fluctuation relative to the mean airway pressure creating sinusoidal pressure fluctuations relative to the mean airway pressure. Hz determines the number of oscillations of delta P per unit time. At lower Hz the ventilator is able to achieve most of the delta P thereby generating effective ventilation and lowering the PCO_2. As the Hz increases the oscillator is unable to achieve the full delta P sinusoidal wave of airway pressure is essentially dampened, reducing the size of the breath, resulting in less effective ventilation. Therefore, keeping the delta P constant and decreasing the Hertz will increase ventilation, and increasing the Hertz will decrease ventilation due to dampening making each delta P less effective.

CLINICAL APPLICATION (FLOW CHART 42.1)

High-frequency ventilation represents an alternative means of ventilatory support in children when conventional ventilation does not work. In a prospective, randomized, crossover study involving 58 children with diffuse lung disease, two groups initially received either high-frequency ventilation or conventional ventilation.[14] Children receiving HFV alone had a better survival (94% vs. 60%), fewer days of supplemental oxygen, and a lower incidence of chronic lung disease (11% vs. 30%), when compared with the control group receiving conventional ventilation. 58 per cent of the patients who did not respond to conventional ventilation and crossed over to HFV survived, whereas 18 per cent crossing over to conventional mechanical ventilation because of persistent respiratory failure survived. Futhermore, improvement in patient outcomes will occur as methods to control the mechanisms of lung injury are studied. Clinical trials involving adults with ARDS using corticosteriods, ibuprofen, prostaglandin E1, monoclonal antibodies against endotoxin, antioxidants, TNF monoclonal antibodies, interleukin receptor antagonist, surfactant and inhaled nitric oxide, will also provide additional adjunctive therapies to improve lung function and minimize the risks of ventilator support.[7]

SUMMARY

High frequency ventilation provides an alternative form of positive pressure support to the critically ill patient with respiratory failure. Current theories in regard to ventilator associated lung injury and strategies of protective ventilation suggest timely initiation of HFV might have a role as a protective strategy. Currently, there is a large effort working towards determining clinical outcomes for HFV and to provide appropriate evidence based rationale to the application of patient management.

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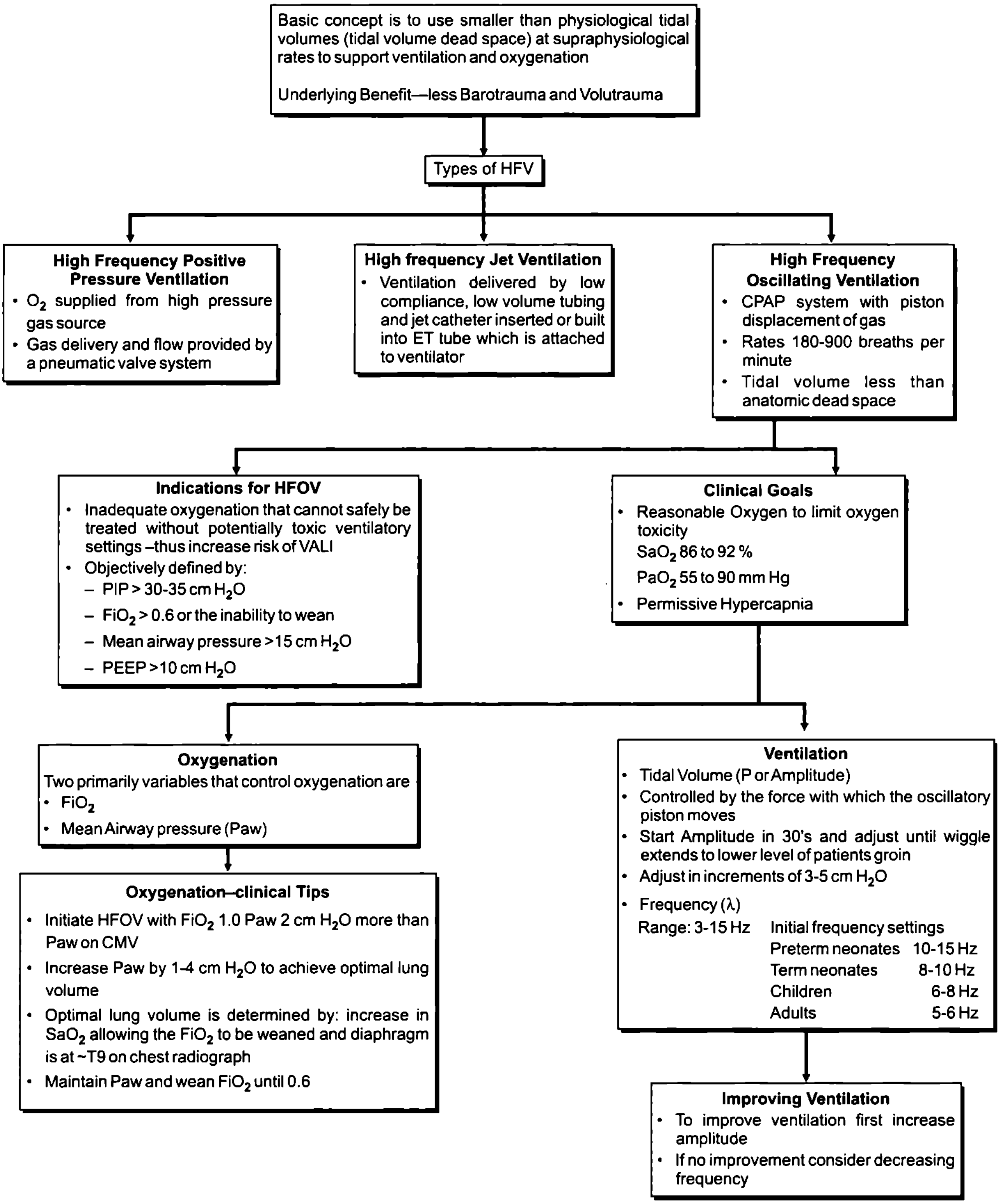
Flow chart 42.1: High frequency ventilation



Basic concept is to use smaller than physiological tidal volumes (tidal volume dead space) at supraphysiological rates to support ventilation and oxygenation

Underlying Benefit—less Barotrauma and Volutrauma

Types of HFV

High Frequency Positive Pressure Ventilation

- O_2 supplied from high pressure gas source
- Gas delivery and flow provided by a pneumatic valve system

High frequency Jet Ventilation

- Ventilation delivered by low compliance, low volume tubing and jet catheter inserted or built into ET tube which is attached to ventilator

High Frequency Oscillating Ventilation

- CPAP system with piston displacement of gas
- Rates 180-900 breaths per minute
- Tidal volume less than anatomic dead space

Indications for HFOV

- Inadequate oxygenation that cannot safely be treated without potentially toxic ventilatory settings –thus increase risk of VALI
- Objectively defined by:
  - PIP > 30-35 cm H_2O
  - FiO_2 > 0.6 or the inability to wean
  - Mean airway pressure >15 cm H_2O
  - PEEP >10 cm H_2O

Clinical Goals

- Reasonable Oxygen to limit oxygen toxicity

  SaO_2 86 to 92 %

  PaO_2 55 to 90 mm Hg
- Permissive Hypercapnia

Oxygenation

Two primarily variables that control oxygenation are

- FiO_2
- Mean Airway pressure (Paw)

Oxygenation–clinical Tips

- Initiate HFOV with FiO_2 1.0 Paw 2 cm H_2O more than Paw on CMV
- Increase Paw by 1-4 cm H_2O to achieve optimal lung volume
- Optimal lung volume is determined by: increase in SaO_2 allowing the FiO_2 to be weaned and diaphragm is at ~T9 on chest radiograph
- Maintain Paw and wean FiO_2 until 0.6

Ventilation

- Tidal Volume (P or Amplitude)
- Controlled by the force with which the oscillatory piston moves
- Start Amplitude in 30's and adjust until wiggle extends to lower level of patients groin
- Adjust in increments of 3-5 cm H_2O
- Frequency (λ)

Range: 3-15 Hz	Initial frequency settings	
	Preterm neonates	10-15 Hz
	Term neonates	8-10 Hz
	Children	6-8 Hz
	Adults	5-6 Hz

Improving Ventilation

- To improve ventilation first increase amplitude
- If no improvement consider decreasing frequency

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PRACTICAL ASPECTS OF HIGH FREQUENCY VENTILATION OF PEDIATRIC AND NEONATAL PATIENTS

High frequency oscillatory ventilation(HFOV) differs from conventional ventilation in that it provides rates of 120 to 1200 with volumes of 0.1 to 1.5 cc/kg. In comparison, conventional ventilation provides rates of 1 to 120 and volumes of 4 to 20cc/kg.

Broadly speaking Indications for using HFOV include: Airleak, to reduce barotrauma, and finally when conventional ventilation is failing.

WHERE IS THE EVIDENCE?

Supporting data for high frequency oscillatory ventilation (HFOV) in acute lung injury are provided by animal studies.[1-7] These studies have demonstrated that HFOV diminishes the amount of ventilator-associated lung injury and improves gas exchange by attenuating alveolar edema and hyaline membrane formation. Comparison of lung-protective strategies of conventional ventilation (CV) and HFOV, in a rabbit model of ARDS, showed that HFOV seems to be associated with less pulmonary inflammation and may protect against biotrauma and ventilator-associated lung injury[7]

Several prospective randomized trials have compared HFOV, as the initial mode of ventilator therapy, with CV in preterm infants who have respiratory distress syndrome.[8-11] Results of these trials have been contradictory and there is no clear evidence that HFOV, compared with CV, offers important advantages.[11] Most studies evaluating HFOV in term neonates have included neonates with unresponsive respiratory failure who are candidates for ECMO (Extra corporeal membrane oxygenation).[12-15] These studies showed that 46-83 percent of these patients responded to HFOV and avoided ECMO. HFOV is now frequently used as rescue treatment for hypoxemic pediatric patients. Some studies of HFOV in patients failing CV strategies have demonstrated improved oxygenation and gas exchange in pediatric respiratory failure.[16-25] Only one prospective, randomized trial of HFOV in pediatric patients who had respiratory failure has been performed.[17] This trial showed that HFOV, using an optimal lung volume strategy, results in significant improvement in oxygenation compared with a conventional ventilatory strategy designed to limit increases in peak airway pressures. Furthermore, HFOV was associated with a lower frequency of barotraumas and improved outcome. In a cohort of pediatric patients submitted to HFOV after failure of CV, HFOV caused significant improvements of oxygenation variables, but patients with preexisting lung disease had a higher rate of ECMO or death than patients with no preexisting lung disease (64% vs 38%).[22] In a more recent retrospective study, survival in 19 pediatric ARDS patients treated with HFOV was significantly better than predicted by the Pediatric Respiratory Failure score but could not be predicted using several outcome scores or the oxygenation index in the first 24 hrs.[23]

In another study,[26] good outcome in 21 pediatric patients with ARDS who received HFOV was associated with lower MAP (before HFOV and at 36 hrs), lower P $(A\text{-}a)O_2$ at 6 hrs, lower OI (oxygenation index) at 24 hrs, and higher PaO_2/FiO_2

at 24 hrs of HFOV. In adult studies, patients failing CV who were then switched to HFOV showed improved oxygenation and ventilation, and HFOV was well tolerated.[27-30] Moreover, the first prospective randomized trial in adults showed a trend toward a decrease in mortality.[29] Despite these encouraging reports, there is not enough evidence to conclude whether HFOV reduces mortality or long-term morbidity in children and adults with acute lung injury or ARDS.[31,32]

In the randomized study by Arnold et al,[17] survival rate was 66 percent in 29 HFOV-treated patients who had a Pediatric Risk of Mortality score of 11.5 and an OI, at enrollment, of 25.5. Eight of these patients (27.5%) were withdrawn from HFOV because hypoxemia, hypercarbia, or severe air leak. Fedora et al.[21] reported a mortality rate of 57 percent among 26 patients with ARDS who had an OI, before HFOV, of 9.6.[29]

In a more recent study,[25] survival rate was 56 percent among 32 pediatric patients with diffuse alveolar disease, failing CV. In the studies by Arnold et al. and Fedora et al.[17,21] mean length of CV was 50 and 143 hrs, and in the study by Slee-Wijffels et al.[25] median length of CV was 29.5 and 63 hrs in the survivors and nonsurvivors, respectively.

In animals studies, there is evidence that HFOV may be more effective when used early in the course of respiratory failure.[31,33] A study by Rosenberg et al.[16] suggested that time spent receiving CV before institution of HFOV may be an important factor related to survival and that prolonged CV may be a poor prognostic sign for a favorable response to rescue therapies. Fedora et al.[21] also reported that the duration of CV before HFOV has a substantial influence on HFOV efficacy and patient survival in children with ARDS. In adult studies,[27,28] the duration of time spent on CV before the start of HFOV was also predictive of mortality. Early intervention with HFOV may be beneficial, perhaps due to the prevention of further ventilator-associated lung injury. In some studies, patients with primary respiratory failure demonstrated a significantly greater risk of improvement on HFOV and had a significantly lower mortality rate (12%) than patients with two and three or more organ failure (67% and 95%, respectively).[19] Sepsis and immunocompromised state were associated with increased risk of death in the study by Arnold et al.[22]

In a recent study on HFOV strategies published in Pediatr Crit Care Med 2006[34] ventilation strategy designed to allow use of HFOV as a relatively early intervention with a goal to reduce ventilator-induced lung injury, showed encouraging results.

Initiation of High Frequency Oscillation

It is important to initiate high frequency ventilation early if conventional methods of ventilation are failing. Impending respiratory failure is indicated by rising carbon dioxide levels and dropping oxygen levels despite ventilator adjustments to compensate.

Respiratory failure is defined as a $PaCO_2$ above 55 and a PaO_2 below 50.

The lung parenchyma in children is especially delicate and the high peak pressures utilized in conventional methods of ventilation can be harmful to the delicate lung tissue.

High frequency ventilation offers the advantage of improved CO_2 removal at lower peak pressures. Barotrauma occurs when the lung tissue is damaged due to the excessive pressures that can be created by conventional ventilation. However, high frequency ventilation can cause hemodynamic changes. This is due to the continuous pressures that are generated by high frequency ventilation,which cause increased pressures in the thoracic cavity.

WHY IS THIS IMPORTANT?

Increased thoracic pressures impede cardiac output. This, in turn, affects the blood pressure, and a vicious spiral can be created. In order to avoid this, it is important to carefully monitor the patient's hemodynamic status. Continuous pressure monitoring is crucial. Arterial lines are necessary when a pediatric patient is placed on high frequency ventilation. In addition to the continuous blood pressure monitoring, the arterial line also functions as the site of numerous blood draws for arterial blood gases. The ideal end results when using high frequency ventilation are no adverse damage to the lungs due to ventilation, and no neurological deficit. Prolonged periods of inadequate oxygenation can cause permanent brain damage.

It is important to know when to implement HFOV.

When Preparing to Change from Conventional to High Frequency Ventilation, What Preparations must be Made?

It is advantageous to have arterial line catheterization established. If the patient is a neonate, this may be an umbilical artery catheter. In pediatric patients, this can be any catheter placed in an artery. In addition, continuous monitoring of vital signs is important:

Monitoring

Blood pressure monitoring is especially important because high frequency ventilation can cause hemodynamic changes such as hypotension and/or decreased cardiac output. If the use of high pressure leads to a decrease in cardiac output, tissue and organ perfusion are affected. By carefully monitoring the urine output, kidney function, and thus organ perfusion, can be monitored.

As thoracic pressures change with the administration of high frequency ventilation, negative effects may result. It is especially important to obtain a chest X-ray (CXR) 30 to 60 minutes after the initiation of high frequency ventilation. This helps to determine whether or not the mean airway pressures are compressing the heart.

Expansion of the chest also must be monitored. The expansion of 8.5 to 9 ribs indicates proper inflation. Adjustments should be made to correct the expansion, as needed. As the lungs heal, they become moreinflated; hyperinflation may lead to pneumothorax. Regular chest films must be taken to determine improvement or decompensation. Initially, chest X-rays should be taken every six hours. The care of patients receiving high frequency ventilation is very individualized. Policies regarding CXR intervals are set by each facility. Nitric Oxide is frequently used in conjunction with HFOV. It is a potent pulmonary vasodilator and works specifically on the pulmonary bed to help improve oxygenation. With increasing use of sidenafil in neonates for PPHN, use of nitric oxide has reduced mostly due to cost related issues

Settings

Amplitude

High Frequency Ventilation is much more dependent on amplitude than on rate. How are the initial settings for high frequency ventilation determined? The first setting to consider is the amplitude, or delta P. The amplitude is similar to the tidal volume in conventional ventilation. The proper setting is determined by observing the patient to see how much chest excursion/movement occurs with oscillation. This **setting should be enough to vibrate or "wiggle" the thorax from the nipple line to the umbilicus.** Settings are changed by 1-2 cm H_2O until the desired amplitude is reached. There is no exact calculation for setting the amplitude. Changes in the amplitude require readjustment of the mean airway pressure.

Frequency

The frequency, which is similar to the rate, is measured in hertz. There are rules by which to choose the setting for the hertz. Multiply the number of hertz times 60 and the exact rate is calculated. Below is a chart for determining initial hertz settings.

This table is taken from the recommendations by Sensormedics for use with the 3100A high frequency oscillating ventilator. Settings depend on the size of the patient and the disease process.

1000 grams	15 Hz
1000-2000 grams	12 Hz
2.0-10 Kg	10 Hz
13-20 Kg	8 Hz
21-30 Kg	7 Hz
> 30 Kg	6 Hz
For Meconium Aspiration Syndrome	3-6 Hz

When initiating high frequency ventilation in the pediatric patient, begin with a hertz such as 6 or 7. This will allow for the greater lung capacity and lung volumes of older patients. Once again, the amplitude should be in accordance with the amount of "wiggle" seen on the chest.When ventilating the pediatric patient, adequate cardiac output must be maintained. The blood pressure must be within acceptable parameters. Without adequate circulation, there cannot be adequate tissue oxygenation.

What Steps are to be Taken if the Blood Pressure is not Adequate?

The first step is a fluid bolus of normal saline. Consider increasing the rate of intravenous maintenance fluids. This should improve blood pressure and cardiac output. If this is not sufficient, vasoactive infusions such as dopamine should be considered. These can be instituted in addition to the increase in intravenous fluids.

Input and output must be continually monitored in order to prevent fluid overload.

Mean Airway Pressure

The mean airway pressure (MAP) is to HFOV as peak airway pressure is to conventional ventilation. **For a severe diffuse alveolar disease, the initial mean airway pressure should be set approximately 2 cm H_2O over what the value for peak pressure was on the conventional ventilator due to high initial opening pressure of alveoli. If compression of the heart is noted on CXR, a decrease in the mean airway pressure is necessary.** The recommended decrease is 0.5 to 1 cm H_2O on the MAP (mean airway pressure) dial. A spontaneous pneumothorax is a complication that can result from high frequency ventilation due to a high mean airway pressures. Optimal pressures are desired at all times with high frequency ventilation. Optimal pressures can be defined as the amount of pressure necessary to ventilate adequately and maintain a normal $PaCO_2$.

FiO_2

An initial FiO_2 is selected to optimize pulmonary vascular resistance while the ventilator is opening the lungs. Use caution when administering high concentrations of oxygen to the neonate.Paralytic agents(muscle relaxants) may cause fluid retention, and this should be taken into consideration. The patient may be paralyzed initially, but paralytics should not be used for an extended period of time. As soon as tolerated by the patient, the agent should be discontinued.

Case Presentations

The following are case presentations of patients with whom high frequency ventilation was used. There is a discussion of how each case progressed and the reasoning behind each decision that was made. Each patient is different and may respond differently to the clinical decisions made. It is important to assess and reassess the patient after each change. Vital signs are normal unless otherwise stated.

Case 1

A 27 week gestational premature infant with an admission weight of 1095 gm is admitted to rule out sepsis. The infant had been delivered to a G2P1 32-year-old mother who had received adequate prenatal care. He is admitted for pneumonia, fever 103'F, and a left upper lobe infiltrate. Upon delivery, the infant's pH is 6.90 and he is intubated with a 2.5 fr endotracheal (ET) tube. Positive pressure ventilation is administered with 100 percent O_2, and he is given intravenous fluids. A repeat umbilical blood gas pH is 7.10. Five meq $NaHCO_3$ are given intravenously and blood cultures are drawn. Intravenous Ampicillin and Gentamicin are given.

Another umbilical blood gas is drawn with results of pH 7.38/CO_2 37/PO_2 111/HCO_3 17/-8.7. An initial dose of Surfactant is given (4.3 cc). This artificial surfactant is useful in immature lungs to help the alveoli stay open, which improves oxygenation.

Upon arrival to the NICU, oxygen saturations are sustained in the 80's by bagging with 100 percent oxygen. The infant is then placed on the high frequency oscillating ventilator with 100 percent O2. Oxygen saturations fall into the 60's and the infant is then re-intubated with a 3.0 endotracheal tube. Nitric Oxide is started at 20 ppm(part per million) for probable persistent pulmonary hypertension secondary to sepsis/pneumonia. Dopamine is started at 5 mcg/kg/min to improve renal function and organ perfusion. APGAR scores are 2 (1 min), 4 (5 min), and 6 (10 min). These are significant because the normal APGAR is 9 or 10.

What would be Appropriate Initial Oscillator Settings? Why?

Initial oscillator settings are: FiO_2 100 percent, Mean airway pressure MAP–17, Amp–26 Hz–15. The correct guidelines for selection of the initial amplitude settings are to deliver enough amplitude to see a"wiggle" from the nipple line to the umbilicus. The FiO_2 should initially be set at 100 percent.

The ABG results on these settings are 7.38/41/45/24/-0.6.

What is the main problem with this blood gas and what intervention(s) need to be taken?

This blood gas shows adequate acid/base balance, but severe hypoxia: the main problem is oxygenation. An increase in the MAP can be instituted to increase oxygenation. This will open the airways more, similar to the way positive end expiratory pressure (PEEP) does in conventional ventilation. The guideline for increasing the mean airway pressures is to increase in increments from 0.5 to 1.0 cm H_2O. The MAP was increased to 18.

Nitric oxide is also started at this time. Nitric oxide is a pulmonary vasodilator and is indicated for the treatment of neonates with hypoxic respiratory failure. It dilates the blood vessels of the lungs so they can carry more oxygen and is used in conjunction with ventilatory support and other appropriate agents.

The follow-up blood gas is 7.28/65/76/30/+1.6.

Interpret this gas and determine the appropriate intervention.

This result reflects an uncompensated respiratory acidosis.

In order to decrease the CO_2, the amplitude is increased to 30.

A repeat blood gas is drawn after the change in HFOV settings. The results are 7.35/51/172/28/+1.7

Is this an acceptable blood gas? Do any interventions need to be made and, if so, what are they?

The amplitude is increased to 32 in order to decrease the CO_2 to within normal limits (35–45). The oxygenation status is excellent, therefore the FiO_2 is decreased to 90 percent. This is a premature neonate; prolonged exposure to high amounts of oxygen has the potential to cause many problems, such as blindness. The ABG results after the changes are made are 7.38/42/74/24/0.2.

Later ABG results are 7.59/27/144/25/+6.0.

Interpret this gas and explain the interventions.

This gas reflects a respiratory alkalosis with hyperoxygenation.

The amplitude is decreased to 22 to allow the CO_2 to rise, and the FiO_2 is further decreased to 80 percent. Suddenly, the oxygen saturation drops to the 70's. The infant is suctioned for a moderate amount of blood. When placed back on HFOV the saturation then falls into the 40's and the heart rate drops to the 80's. A large amount of frank blood is suctioned from the ET tube. Epinephrine is instilled into the endotracheal tube to assist in hemostasis. A portable chest X-ray is taken.

What is causing the above condition?

Due to the sudden onset of hemodynamic changes a pneumothorax is suspected and the portable ches X-ray shows a large left pneumothorax.

A 10fr chest tube is place in the fourth intercosta space, mid-axillary, with an audible resolution o the pneumothorax. Epinephrine is a vasoconstricto and is used in this situation to slop bleeding in th lungs. Any time intrathoracic pressure increases there is an increased risk for pneumothorax. As th mean airway pressures are increased, the risk fo potential negative side effects are increased; the lun tissue in premature neonates is very delicate.

The ABG results after chest tube placement ar 7.31/35/129/18/-8.0. Interpret this gas and give th intervention. This is a partially compensate metabolic acidosis with hyperoxygenation.Thi acidosis has already been partially compensated fo by blowing off CO_2 and now must be treate pharmacologically.

Sodium bicarbonate is given intravenously. A the pneumothorax resolves, the infant is weaned o high frequency ventilation. As the neonate grow so does the lung tissue. The infant is able to b changed to conventional ventilation and late extubated. He is then placed on oxygen via nas cannula at an FiO_2 to maintain the oxygen saturatio greater than 92 percent. The infant is discharge thirty days after extubation.

Case 2

A 14-year-old female is admitted with a decrease level of consciousness and abdominal bleeding. S also complains of abdominal pain, diaphoresis, a cramping in the left upper quadrant and periumbilic area. A diagnostic laparoscopy is performed, noti copious bleeding from a hemorrhagic cyst. S experiences hypotension and a decreased hem globin and hematocrit. Packed red blood cells a transfused. After fluid and blood resuscitation, exploratory laparotomy is performed. A 2000 hemoperitoneum with a small amount of bleedi from the right ovary is discovered.

The initial ABG on room air is 7.32/52/68/26.

What is happening? From the given data, is h condition prone to deteriorate? What are app priate initial ventilator settings?

This blood gas indicates a potential for respiratory failure. The CO_2 level is higher than normal without any form of compensation. Due to this lack of compensation, we determine that this is an acute event.This patient is intubated to protect her airway. Because of the potential for respiratory failure, it is preferable to intubate as an elective procedure, rather than as an emergency measure during an arrest situation. This patient has a great risk for hemorrhagic shock because of the amount of blood loss from the cyst. Close monitoring of the hematocrit and hemoglobin is important. In addition, it may be necessary to place an arterial catheter for continuous blood pressure monitoring and laboratory draws.

Despite all efforts using conventional ventilation via pressure regulated volume control (PRVC), a marked decrease in the PaO_2 ensued. PRVC is a mode of ventilation with the Servo 300 that allows volume ventilation with minimal pressures. This minimizes barotrauma, but ventilates very effectively in difficult to ventilate patients. **The ABG results are 7.47/31/54/22/+1.0 on settings of: rate- 20, tidal volume- 350, and FiO_2- 100 percent.**

Is this a ventilation or oxygenation problem?

The pH is normal, the $PaCO_2$ is only slightly below normal, and the PaO_2 is 54; this is clearly an oxygenation problem.

High frequency oscillation ventilation is initiated due to the need to minimize the insult to the lungs and try to recruit more alveoli and improve oxygenation.

What would be appropriate initial settings for HFOV?

Initial ventilator settings are FiO_2 100 percent, Hz 6.5, amp 45, and MAP 35.

The amp setting is set just high enough to cause a wiggle from the nipple line to the umbilicus.The amp setting is set just high enough to cause a wiggle from the nipple line to the umbilicus.

The initial ABG results are: 7.32/48/203/25/-1.5.

What should be done next?

Oxygenation has improved, but the $PaCO_2$ is increasing while the pH is decreasing. This is indicative of respiratory acidosis.The goal here is to decrease the CO_2. Hyper-oxygenation is not necessary.

What is necessary to achieve this goal?

First, a decrease in the FiO_2 is necessary to bring the PaO_2 nearer to normal.

Increasing the amplitude will help decrease the $PaCO_2$.

Her condition seems to be stabilizing.

The next ABG that is drawn shows the results: 7.04/113/376/30/-4.8.

Does this ABG indicate acidosis or alkalosis; metabolic or respiratory? What interventions should be taken?

Should sodium bicarbonate be given? Why, or why not?

The last blood gas indicates a severe respiratory acidosis. Because the bicarbonate level is 30, there is little metabolic involvement. In fact, the bicarbonate levels have started to rise to help the pH increase. In other words, there is some compensation. This is having no effect on the pH, which is still grossly abnormal.

Sodium bicarbonate is not indicated for this blood gas because the cause is respiratory, not metabolic.

A chest X-ray is taken at this time and reveals rib expansion to the eighth rib. The mean airway pressures will expand the lungs to various rib expansions. The patient is suctioned for a large amount of thick secretions. The MAP is increased and the repeat ABG results are 7.13/93/225/31/+1.5.

What does this indicate? What are the options for the ventilator?

Because the rib expansion should include 8.5 – 9 ribs, the MAP is increased to help improve oxygenation.In addition, the Hz may also be decreased to lower the CO_2. The Hz is decreased to 5 and the amp is increased to 50.

This will allow a faster rate and larger tidal volume.

The repeat ABG is 7.16/66/314/23/-7.0.

The MAP is then decreased to 27.7 and the Hz is decreased to 4. The repeat ABG is 7.34/50/128/27/+1.0

Do you agree with these changes? Why?

The MAP was decreased due to evidence of hyper-oxygenation. To lower the CO_2 even more, the Hz was decreased. As this case progresses over the next five days, the FiO_2 and the MAP are weaned gradually.

When would be an appropriate time to switch to conventional ventilation? Why?

The goal is to wean the mean airway pressure lower. When the mean airway pressure is about 5 cm H_2O over what it was on conventional ventilation, it is time to change ventilation modes. The amplitude setting is another indicator that it is time to switch to conventional ventilation. As the patient recovers, the amplitude is weaned. This indicates that the lungs are healing and recovering. It is then time to change the mode of ventilation to a conventional mode. When the amplitude is weaned to a low number, such as 18 or 20, it also indicates it is time to change to conventional ventilation. When placing the patient back on conventional ventilation, the settings might be temporarily higher to allow the patient to compensate for the change in ventilator modes.

Take Home TIPS

Ventilation to high frequency, remember these tips:

1. Set the MAP at 2-4 cm H_2O over the value used on conventional ventilation.
2. Set the amplitude to see a "wiggle" from the nipple line to umbilicus.
3. Set the hertz according to table listed.
4. Set the FiO_2 at 100 percent.
5. Obtain a chest X-ray approximately 30-60 minutes after the initiation of high frequency ventilation.
6. The rib expansion on X-ray should involve 8.5 – 9 ribs.
7. Obtain frequent arterial blood gasses to monitor progress.
8. Break the circuit only when absolutely necessary. Suction the endotracheal tube as necessary.
9. Wean the ventilator settings as tolerated.

Is there another way of practice of HFOV?

Different institutions have different protocols, but the essential principles and goals remain same:to provide gentler ventilation with least barotrauma and FiO_2 causing least hemodynamic compromise.

Following is a protocol from Stanford hospital and clinics respiratory care services:

STANFORD Hospital and Clinics Recommendations and Guidelines for Implementation of High Frequency Oscillatory Ventilation (HFOV)

Indications and Patient Selection

1. Patients with severe ARDS requiring an FiO_2>0.60 with a mean airway pressure (Pmaw) > 24 cm H_2O may be considered for a trial of HFOV if a "lung protective" target Pplat < 30 - 35 cm H_2O cannot be maintained with pressure control ventilation. In practice, patients considered for HFOV have generally been tried on "high" PEEP and/or pressure control ventilation (PCV) with extended inspiratory times to raise Pmaw. A Pmaw =24cm H_2O while on conventional ventilation is a reasonable threshold to consider changing to HFOV. Early institution of HFOV in patients deteriorating on conventional mechanical ventilation may be important to improved survival, although this has not yet been rigorously established.
2. Failure to improve the oxygenation within the first 24 –48 hours is indicative of a poor response to HFOV, which may be prognostic for a decreased likelihood for survival. For example, patients with late phase fibroproliferative ARDS, when the alveolar architecture is severely damaged, are less likely to respond.

Patient Preparation

1. Prior to starting a patient on HFOV, it is imperative that the patient's airway is suctioned and known to be patent. If fiberoptic bronchoscopy is indicated, it should be performed before initiating HFOV.
2. Ensure adequate titration of sedation, analgesia, and neuromuscular blockade while the patient is still on conventional ventilation. The patient's intravascular volume status should be reassessed given that a higher Pmaw will be used with HFOV, leading to the potential for hypotension secondary to elevated intrathoracic pressures and reduced preload IV.

Initial HFOV Settings

1. **Oxygenation**:
   The main determinant of oxygenation during HFOV is the Pmaw, which is generally initiated at 5 cm H_2O higher than the Pmaw noted during conventional ventilation. Hemodynamically unstable patients may be started on a Pmaw either the same or 2-3 cm H_2O above Pmaw during conventional ventilation. Brief hypotension shortly after starting HFOV is usually managed with a trial of fluid boluses to improve preload. FiO_2 is usually set at 1.00 after the transition to HFOV, and then tapered using oximetry guidance to maintain SpO_2 >90 percent. If the SpO_2 (or PaO_2) has not improved enough to allow weaning of FiO_2, the Pmaw is raised in 2-3 cm H_2O increments at 30 – 60 minute intervals in the hopes of improving lung recruitment. The time course of oxygenation change after initiation of HFOV (or after increasing Pmaw) is variable. Some patients may slowly improve oxygenation only after a period of several hours. Vigilance and patience are required during the early phase of treatment. The maximum Pmaw generally obtained with the SensorMedics 3100B is 45 – 55 cm H_2O. Patients with large bronchopleural fistulas or endotracheal cuff leaks may have difficulty achieving a desired Pmaw without increasing the bias flow. In some patients with very severe air leaks, a maximum bias flow (60 lpm) may be required.
2. **Ventilation:**
   The main determinants of $PaCO_2$ elimination are the pressure amplitude of oscillation (P) and the frequency setting (hertz). Increasing the amplitude and decreasing the frequency (Hz) will increase the delivered tidal volume and lower the $PaCO_2$. Conversely, decreasing amplitude and increasing frequency (Hz) will reduce delivered tidal volume and allow $PaCO_2$ to rise. The amplitude is generally initiated at either a value where the patient's chest vibrates down to their mid-thigh. Alternatively, initial amplitude may be set to observe adequate "chest wall vibration". Initial frequency is usually set at 5 Hz. Patients who demonstrate rapidly rising $PaCO_2$ on HFOV should have aggressive increases in amplitude (10 to 20 cm H_2O) and reduced Hz to the lowest value achievable (3 Hz on the SensorMedics 3100B). An adjunct to improving $PaCO_2$ elimination is to briefly disconnect the patient from HFOV and vigorously manually ventilate with a PEEP-valve equipped bag. Aggressive action is required for a rapidly rising $PaCO_2$ during initiation of HFOV because improvements in $PaCO_2$ do not occur as quickly as when changes are made to conventional ventilators. An ABG should be drawn 15 to 20 minutes after starting HFOV to determine the trend of the $PaCO_2$. Subsequent ABG's are generally obtained at 30 to 60 minute intervals until stabilization occurs.

Guidelines for Initial HFOV Settings

1. Prior to initiating HFOV, perform a recruitment maneuver on the oscillator by increasing Paw to 40 cm H_2O for 30-40 seconds. NOTE: the oscillator should be OFF during the maneuver. Immediately abort the maneuver if hemodynamic compromise occurs.
2. Set initial Paw at 5 cm H_2O above conventional ventilator Pmaw.
3. Set power to achieve initial amplitude at chest oscillation to mid-thigh.
4. Set Hz at 5. Set IT to 33 percent (may increase to 50% if difficulty with oxygenation; this may further raise carinal pressure an additional 2-4 cm H_2O).
5. If oxygenation worsens, increase Pmaw in 2-3 cm H_2O increments q 30 minutes until maximum setting (approximately 45-55 cm H2O).
6. If $PaCO_2$ worsens (but pH > 7.2), increase amplitude in 10 cm H_2O increments q 30 minutes up to the maximum setting. After maximum amplitude is achieved, if necessary, decrease Hz to the minimum setting of 3 Hz.
7. If severe hypercapnea occurs, with pH < 7.2, bag patient, set maximum amplitude, Hz at 3, and try a small cuff leak (5 cm H_2O and then compensate bias flow); rule out endotracheal tube obstruction.
8. If oxygenation improves, gradually wean FiO_2 to 0.40, then slowly reduce Pmaw 2-3 cm H_2O q 4 – 6 hours until 22 – 24 cm H_2O range.
9. When the above goal is met, switch to PCV (initial settings: peak pressure titrated to achieve delivered VT 6 ml/kg IBW, Pplat < 30 - 35 cm H_2O), I:E 1:1, PEEP 12 cm H_2O, rate 20 – 25, Paw should be 20 cm H_2O (+/- 2 cm H_2O).

Weaning from HFOV

The principal goal of using HFOV in treating patients with ARDS is to achieve a nontoxic FiO_2 (<0.60) while minimizing ventilator induced lung injury. When patients respond with improved oxygenation, the first weaning maneuver therefore is to reduce the FiO_2 before any reduction is considered in Pmaw. A reduction of FiO_2 to 0.40 with a target $SpO_2 > 90$ percent before attempting reductions in Pmaw is recommended. If the patient can maintain a $SpO_2 >$ 90 percent on a FiO_2 0.40, a gradual reduction of Pmaw (e.g. decrease 1- 2 cm H_2O q 30 minutes as tolerated) should be attempted. If the SpO_2 decreases during Pmaw reduction, resume the previous Pmaw that was able to maintain a $SpO_2 > 90$ percent on FiO_2 0.40. Perform an ABG and CXR for every total Pmaw reduction of 5 cm H_2O. **Once a Pmaw of 20 – 24 cm H_2O has been achieved while maintaining a FiO_2 of 40 percent, the patient can be switched back to a trial of conventional ventilation.** Obtain an arterial blood gas 15-20 minutes after transfer to conventional ventilation to guide further ventilator adjustments.

Potential Complications

1. **Hypotension:**
   Occasionally, patients will develop hypotension shortly following transfer to HFOV or as Pmaw is raised. This usually implies relative hypovolemia and responds to intravenous fluid boluses and/or vasopressors as indicated.
2. **Pneumothorax:**
   Tension pneumothorax occurring during HFOV may not cause changes to the displayed Pmaw or amplitude as the patient develops progressive hypotension and desaturation. A high index of suspicion is necessary for pneumothorax and confirmation (if time permits) requires an immediate CXR. It may be difficult by auscultation alone to detect the side of the pneumothorax during HFOV secondary to background noise of the ventilator and the diffuse transmission of airway sounds. The visual loss of chest oscillation that usually occurs on the affected side may provide an important physical sign.
3. **Endotracheal tube obstruction:**
   Subtotal occlusion of the endotracheal tube may result in refractory hypercapnea. An abrupt rise in $PaCO_2$ and loss of visual chest oscillation in an otherwise stable patient may be secondary to an obstructed or narrowed endotracheal tube. A suction catheter should be passed immediately to ensure patency of the endotracheal tube.

CONCLUSION

Ventilation strategy should be designed to avoid exposure to prolonged aggressive conventional ventilation and to **use HFOV as a relatively early intervention**, with a goal to reduce ventilator-induced lung injury and occurrence of intractable respiratory failure. Clinical objectives in the management of acute lung injury and ARDS focus on the prevention of ventilator-associated lung injury through lung protective strategies, using small tidal volumes and high positive end-expiratory pressure levels. HFOV offers the potential to maintain adequate gas exchange without imposing the large pressure swings and tidal volumes associated with ventilatory-induced lung injury.

However, randomized controlled trials are needed to identify its benefits over conventional modes of mechanical ventilation and to establish the optimum timing of HFOV initiation.

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APPENDIX

High frequency ventilation: Management Strategies with High Frequency Ventilation in Neonates and children Using the SensorMedics 3100A High Frequency Oscillatory Ventilator

Sensor Medics Oscillatory Ventilator 3100A

A true high frequency oscillator with a diaphragmatically-sealed piston driver. Theoretically capable of ventilating patients up to 30 kg. Tidal volume typically delivered approximately 1.5-3.0 cc/kg (< dead space). Extremely efficient ventilation secondary to active expiratory phase, but not capable of delivering sigh breaths.

I. INITIAL SETTINGS

A. **Frequency**: Set initially at 10 Hz (600 BPM) for term infants and 15 Hz (900 BPM) for premature infants (< 2.5 kg). For children between 6-10 kg, use 8 Hz, between 10-20 kg, use 6 Hz and between 20-30 kg, use 4 Hz for an initial setting.

B. **Inspiratory time (IT):** Set initially at 33 percent (e.g. 22 msec at 15 Hz, 41 msec at 8 Hz, 55 msec at 6 Hz).

1. Warning - The per cent of I.T. should never be increased because it will lead to air trapping and fulminant barotrauma. Total I.T. should only be increased by decreasing frequency, thus leaving the I:E ratio constant. I.T. can be decreased to 30 percent to heal airleaks.
2. I:E ratio: 1:2 (3-15 Hz), at 33 percent I.T.

C. **Power:** A rough representation of the volume of gas generated by each high frequency wave. Range (1.0 - 10.0). Maximum true volume of gas generated by the piston is 365 cc. Maximum amplitude or volume delivered is highly variable and depends on the following factors: circuit tubing (compliance, length and diameter), humidifier (resistance and compliance - water level), ET tube diameter and length (FLOW is directly proportional to r^4/l, where r = radius of airway and l = length of airway), the patient's airways and compliance.

1. Set the POWER initially 2.5 if wt <2.0 kg, 3.0 if wt 2-2.5 kg, 4.0 if wt 2.5 - 4.0 kg, 5.0 if wt 4.0 - 5.0 kg, 6.0 if wt 5-10 kg, 7.0 if wt 10-20 kg. Chest wall needs to be vibrating. If not vibrating, increase power.
   Check ABG's every 15-20 min until $PaCO_2$ is 40-60, i.e. titrate POWER setting based on $PaCO_2$ desired. Many HFOV centers have you order amplitude or delta P to regulate ventilation instead of power. We have decided that the Power setting is a more reliable way of adjusting this ventilator and thus we order changes in power in order to regulate ventilation.
2. Alveolar ventilation is directly proportional to POWER, therefore the level of $PaCO_2$ is inversely proportional to the power.
3. During HFOV, alveolar ventilation (Ve) = $(TV)^2f$ as compared to CMV where Ve = TV(R). Thus we primarily adjust the power (amplitude) to change tidal volume in order to manipulate ventilation.
4. *Management of ABG's (Ventilation - Ve):*
   a. Change POWER by 0.2-0.3 to change CO_2 ± 2-4 mm Hg
   b. Change POWER by 0.4-0.7 to change CO_2 ± 5-9 mm Hg
   c. Change POWER by 0.8-1.0 to change CO_2 ± 10-15 mm Hg
   d. *Warning:* It is extremely important to normalize $PaCO_2$ rapidly by weaning Power in order to avoid volutrauma from excessive tidal volumes. Thus check ABG's frequently (Q15-20 min) and decrease POWER accordingly until $PaCO_2 > 35$. $PaCO_2 < 35$ correlates with an increased risk of pneumothorax. Thus to minimize the risk of volutrauma, it is important to use the least amount of TV (POWER or AMPLITUDE) possible to achieve ventilation.
   e. If $PaCO_2$ still remains elevated at high POWER setting (>8.0), decrease FREQUENCY by 2 Hz every 15-20 min until maximum tidal volume is reached (3-4 Hz at a POWER of 10.0). The lower frequency leads to a longer I.T. which results in a larger tidal volume of gas displaced towards the infant. This increased TV leads to increased alveolar ventilation (on HFOV, Ve = $(TV)^2f$.
5. *Manual ventilation:* Hand bagging while on the SensorMedics Ventilator should be avoided secondary to the risk of barotrauma due to over distention. Suctioning should be performed using just the ventilator breaths alone (an inline suctioning adapter would be best). If bagging has to be done, the PIP while bagging should not exceed 8-10 cm above the MAP and a PEEP of 6-8 cm should be maintained as tolerated.

D. **MAP:** Oxygenation on HFOV is directly proportional to MAP which is similar to CMV, however with the SensorMedics HFOV all of the MAP is generated by PEEP. Thus during HFOV:MAP=PEEP.

1. Initial Settings:
   a. Neonates - Initial MAP should be 2-4 cm above the MAP on CMV.
   b. Infants/Children - Initial MAP should be 4-8 cm above the MAP on CMV.
   c. If starting immediately on HFOV use a MAP of 8-10 cm in neonates and 15-18 cm in infants/children.
2. Management of ABG's (Oxygenation a MAP):
   a. If not oxygenating adequately at initial MAP (12-18 cm) obtain CXR to assess lung volume. If lung is not hyperinflated (flattened diaphragm) or is below optimal lung volume 9-10 ribs then increase MAP

by 2-4 cm every 20-30 min until adequate oxygenation is achieved or lung starts to become overinflated (e.g. FiO_2 0.6-0.7 increase by 2-4 cm, FiO_2 1.0 increase by 4-8 cm).

  b. Maximum potential MAP = 40-45 cm
  c. Warning: If oxygenating adequately, but the lung is hyperinflated immediately decrease MAP by 1-2 cm every 2-4 h until lung volumes return to normal. If the lung is allowed to remain hyperinflated for prolonged periods of time the risk of barotrauma increases dramatically.
  d. If not oxygenating with lung becoming hyperinflated, you can decrease frequency as a way to increase I.T. while keeping I:E ratio constant.

II. MANAGEMENT STRATEGIES FOR THE SENSORMEDICS 3100

The SensorMedics HFOV is usually used for premature infants, term infants or young children with respiratory failure not responsive to CMV. The Infant Star HFV with its ability to oxygenate using less MAP than the SensorMedics due to the use of an occasional sigh breath (1-4 per min) is also recommended for premature infants with respiratory failure.

A. **Term infant with severe respiratory failure (PPHN, MAS, GBS pneumonia, RDS):** Start at a frequency of 10 Hz and a Power of 3.0 to 5.0. Initial MAP 4 cm above MAP while on CMV. Check CXR 2 hrs after converting to HFOV, then adjust MAP to achieve optimal lung volume (9-10 ribs expanded). If not oxygenating, increase MAP by 2 cm every hour until oxygenation improves. Adjust Power to keep $PaCO_2$ 45-55.

B. **Airleaks:** Pneumothorax or PIE - The goal is to minimize both tidal volumes and peak pressures generated by any given TV. Tolerate increased FiO_2 requirements (0.6 - 1.0) in order to keep MAP at a minimum. Practice permissive hypercarbia and accept high $PaCO_2$'s to minimize the TV. Use a FREQUENCY of 12-15 Hz in order to minimize both total I.T. and TV in order to heal the airleak. Also decrease I.T. to 30 percent.

C. **ARDS:** The goal is to minimize volutrauma, barotrauma and oxygen toxicity. Thus use the minimum POWER possible at the appropriate FREQUENCY in order to keep $PaCO_2$ adequate (e.g. 55-65 mm Hg). Increase MAP as high as necessary to keep $FiO_2 < 1.0$. Also decrease frequency to increase I.T. to improve oxygenation.

D. **RDS:** Give surfactant replacement therapy using manual bagging. Start with frequency of 15 Hz, I.T. of 33 percent. Use MAP of 8-10 cm or 2 cm above MAP on CMV. Wean FiO_2 until <0.50 then MAP as tolerated to avoid overinflation. Wean power/amplitude to keep $PaCO_2$ 45-60 mmHg. Follow blood gases q30-60 min after surfactant until stable and wean appropriately to avoid hypocarbia.

E. **Rescue Therapy For Premature Infant With RDS:** To be used for premature neonates who can't ventilate on either CMV or the Infant Star HFV or who require a MAP > 20 cm to achieve oxygenation while on the Infant Star. Use initial frequency of 15 Hz, Power of 3.0 - 4.0, MAP 2 cm above MAP on the Infant Star HFV, or MAP 4 cm above the MAP on CMV.

F. **BPD:** The goal is to minimize volutrauma, barotrauma, atelectatrauma, biotrauma and oxygen toxicity. Use minimum power/amplitude to keep $PaCO_2$ adequate (e.g., 50-70 mmHg). Increase MAP as necessary to keep FiO_2 <0.50 if possible. Use I.T. of 33 percent. Use frequency of 10-15 Hz: use the lower frequencies if having difficulty with oxygenation, use the higher frequencies if having problems with hypocarbia or PIE.

G. **Other potential indications:** CHF/Pulmonary Edema, Chest Physiotherapy, Hypoplastic Lungs and Post-op Heart Patients

H. **Not beneficial for asthma:** Increased risk of air trapping with reactive airway disease.

III. WEANING

A. **Oxygenation:** Once oxygenation is adequate and the patient is ready to be weaned follow these steps:
  1. First only wean FiO_2 until < 0.60 unless hyperinflated.
  2. Once FiO_2 < 0.60 or hyperinflated, decrease MAP by 1 cm Q4-8h; if OXYGENATION is lost during weaning then increase MAP by 3-4 cm to restore lung volumes and begin weaning again, but proceed more slowly with decreases in MAP.
  3. Minimal MAP is 8-16 cm with FiO_2 < 0.50, at this point one can convert to CMV or remain on HFOV while the patient continues to heal (e.g., 8-12 cm < 2.5 kg, 13-16 cm > 2.5 kg).

B. **Ventilation:** Reduce POWER by 0.2-0.3 units per change whenever $PaCO_2$ decreases below threshold, until minimal POWER is reached (1.5-4.0) depending on the size of the patient. If frequency is below the standard frequency for the patient's weight, then first wean by increasing frequency back to baseline which also decreases the tidal volume, then decrease power as described.
  1. Extubation - Neonates are ready to be extubated for a trial of NPCPAP when they meet the following criteria:
    a. MAP < 10 cm, FiO_2 < 0.40 and power < 2.5 then use NPCPAP of 7-9 cm.
  2. Conventional Ventilation - Term neonates are ready for conversion to conventional mechanical ventilation (IMV or SIMV) when they meet the following criteria:
    a. MAP < 16-17 cm, FiO_2 < 0.40 - 0.45 and power < 4.0
    b. To convert to conventional mechanical ventilation (CMV) use MAP 3-4 cm less than the MAP on HFV [e.g., MAP = 16-17 on HFV, use a MAP of 12-13 on CMV (PIP = 26, PEEP = 8, Rate = 40, IT = 0.4)].

IV. COMPLICATIONS ASSOCIATED WITH HFOV

A. Hyperinflation or Barotrauma: increased MAP.

B. Secretions: a suctioning.

C. Hypotension: increase MAP, and rule out other causes (e.g., pneumothorax, sepsis, dehydration, etc.).

Courtesy: Jonathan M. Klein, M.D. Iowa Neonatology Handbook

CHAPTER

Inhaled Nitric Oxide (INO)

Reeta Singh, Praveen Khilnani

Since the discovery of endothelium derived relaxing factor and its subsequent identification as nitric oxide,[1] recognition of its potent vasodilator properties and its unique ability to be delivered as a gas to the lung, inhaled nitric oxide (INO) has become an exciting new treatment for several disorders, characterized by pulmonary hypertension and pulmonary vasoregulation.

Endogenous NO

NO is produced by L- argine by a family of enzymes called nitric oxide synthase (NOS) which exist in constitutive and inducible forms.[2] Constitutive NOS is always present, is calcium dependent and produce low levels of NO intermittently, which is a major endogenous regulator of vascular tone. In contrast the inducible NOS is activated by cytokines and endotoxins, once induced it produces large amounts of NO. The pathophysiological role of this nitric oxide is evident in a variety of disease including septic shock, asthma, and reperfusion endogenous injury, etc (Fig. 43.1).

Clinical Pharmacology of INO

NO binds rapidly to iron in haem moiety of proteins such as guanyl cyclase, hemoglobin and electron transport chain. Activation of guanyl cyclase results in production of cyclic guanosine monophosphate (cGMP) which leads to vasodilation, and relaxation of smooth muscles of cardiovascular, respiratory, gastrointestinal and genitourinary system. Because it binds to haem, it gets inactivated in blood and does not enter systemic circulation. This accounts for selective effect of INO on pulmonary circulation.[3]

INO appears to increase the partial pressure of arterial oxygen (PaO_2) by dilating pulmonary vessels in better ventilated areas of the lung, redistributing pulmonary blood flow away from lung regions with low ventilation/perfusion (V/Q) ratios towards regions with normal ratios.

Persistent pulmonary hypertension of newborns (PPHN).

At birth, the pulmonary circulation changes dramatically. Pulmonary blood flow increases 8-10 fold and pulmonary arterial pressure decrease to less than half systemic levels in the first 24 hours of life.[4,5] Although release of vasoactive mediators, increased oxygenation, establishment of an airliquid interface have been shown to play a central role in transition of pulmonary circulation,[6] if postnatal adaption of pulmonary circulation does not occur, a clinical syndrome, PPHN results.

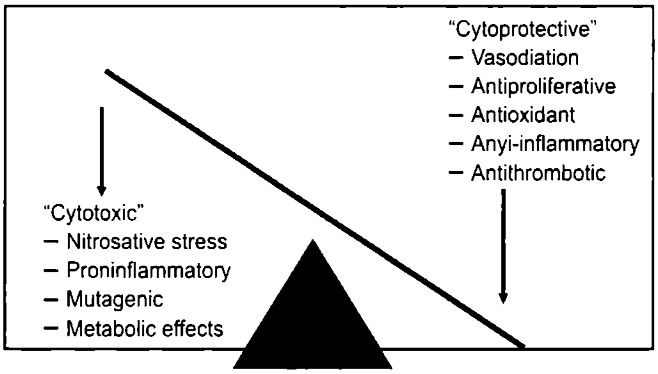

Fig. 43.1: Inhaled nitric oxide therapy: A balance between cytoprotective and cytotoxic effects

It is characterized by extrapulmonary right to left shunting across the foramen ovale and ductus arteriosus, pulmonary hypertension and severe central hypoxemia, that is not responsive to high concentrations of inspired oxygen. PPHN is often complicated by parenchymal lung injury, such as meconium aspiration, pneumonia and surfactant deficiency, further compromising efforts to improve oxygenation.

When other therapies fail neonates are treated with extracorporeal membrane oxygenation.[7] This therapy improves survival in neonates with respiratory failure, but its administration is labor-intensive and costly and necessitates large amounts of blood products. The mortality rate in neonates treated with extracorporeal membrane oxygenation is 15-20 per cent and 10-20 per cent of the neonates, whose survive have substantial developmental delay.[8] Effective treatment has been limited by the absence of a selective pulmonary vasodilators. Intravenous vasodilator agents can cause non-selective vasodilation, resulting in worsening of intrapulmonary shunting and systemic Hypotension.[9] Neonates with PPHN might be hypoxemic from a combination of intrapulmonary shunting secondary to parenchymal lung disease and extrapulmonary shunting secondary to increased pulmonary vascular resistance with or without myocardial dysfunction. INO (Fig. 43.2) acutely improves oxygenation in most- term and near term neonates by reversal of extrapulmonary right to left shunting of blood secondary to pulmonary vasodilation and also improves VQ matching secondary to redistribution of pulmonary blood flow to well ventiiated lung regions.[4,5]

Fig. 43.2: Nitric oxide delivery system

Clinical trials indicate that need for ECMO is diminished by INO[10] (Fig. 43.3). Responsiveness to INO in these patients is dependent on the primary disease or physiologic cause of hypoxemia, with the best response rates observed in patients with idiopathic PPHN.[11] In neonates with severe parenchymal lung disease, responsiveness to INO can be improved by therapies that enhance lung recruitment, especially during high frequency oscillatory ventilation (HFOV). The combination of HFOV and INO can be efficacious in patients who fail to respond to either therapy alone.[12]

Doses

Experimental data support the notion that the minimally effective doses of INO should be used. At high concentrations INO can react with oxygen to form dioxygen nitrite (NOO), which has been shown to cause surfactant destruction.

The recommended dose is 10 to 20 part per million (ppm).[10,13] When dose is increased to 80 ppm, if the improvement in PaO_2 was less than 20 mmHg, increased incidence of methemoglobinemia occurs without any increase in PaO_2.[14] At the same time administration of a subtherapeutic (2 ppm) dose of INO may adversely affect the clinical response to a

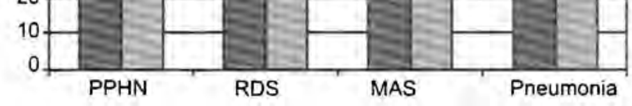

Fig. 43.3: Percent survival without ECMO by disease category in a controlled trial of INO occurred in newborns with PPHN or pneumonia RDS–Respiratory distress syndrome. MAS–Meconium aspiration syndrome, PPHN–Primary pulmonary hypertension

(Source: Neonatal inhaled Nitric Oxide study group)

subsequent therapeutic doses of INO.[15] Clark et al used INO at 20 ppm for 24 hours followed by 5 ppm for next 96 hours and requirement for subsequent ECMO was reduced.[16] Figure 43.1 shows the nitric oxide delivery setup with dial regulator of PPM dose of INO.

Duration of Treatment

No controlled data are available to determine the maximal safe duration of INO therapy. In multicenterclinical trials of INO, the typical duration of INO has been less than 5 days, which parallels the clinical resolution of PPHN, [16] If INO is required for longer than 5 days, other causes like pulmonary hypoplasia must be excluded. INO can be discontinued if the fraction of inspired oxygen is less than 0.6 and PaO_2 is more than 60 without evidence of rebound pulmonary hypertension or an increase in FiO_2 more than 15 percent after INO withdrawal.[13]

Weaning

Sudden withdrawal can be associated with life-threatening elevation of pulmonary vascular resistance, profound desaturation and systemic hypotension caused by decreased cardiac output. Exogenous NO may down regulate endogenous NO production, which contribute to severity of pulmonary hypertension after INO withdrawal. To avoid these rebound effects numerous approaches have been used and INO should be reduced in a step wise fashion.[17]

Unresponsiveness to INO Therapy in PPHN

Many neonates have only partial or transient improvement in oxygenation during INO therapy. INO tends to increase PaO_2 more readily in idiopathic PPHN than in patients with congenital diaphragmatic hernia.[17] Its use in hypoxemic neonates without pulmonary hypertension.

Unresponsiveness to INO[18] is commonly seen in following situations:

1. INO use in hypoxemic neonates without pulmonary hypertension.
2. Inability to deliver NO due to poor lung inflation.
3. Unsuspected or missed anatomic cardiovascular lesions.
4. Alveolar capillary dysplasia is a very rare cause for PPHN and is characterized by a developmental abnormality in the pulmonary vasculature. Despite aggressive therapy with NO and ECMO survival is rare.[19]
5. Advanced vascular remodeling or severe lung hypoplasia.

In some cases, INO therapy reverses right to left shunting but hypoxemia may persist due to intrapulmonary shunt, suggesting underlying disease. In these situations changes in conventional ventilator management or HFOV can further improve PaO_2 by improving lung inflation and may decrease the need for ECMO.[11] In many cases greater improvement is achieved with INO in combination with either therapy alone.[19]

Monitoring

Methemoglobinemia occurs after exposure to high concentration of INO. This complication has not been reported at lower doses. However, because methemoglobin reductase deficiency may occur unpredictably, it is reasonable to measure methemoglobin level by co-oximetry within four hours of starting INO therapy and subsequently at 24 hour intervals.

Transport with INO

Although INO therapy is often effective, 30-40 per cent of sick newborns do not have sustained improvement in oxygenation and hemodynamics after the initiation of therapy often require transport to ECMO center. Abrupt discontinuation may be dangerous and availability of NO during transport is vital.

Long-term outcomes of neonates treated by INO has been studied widely, preliminary studies show no excess adverse health or neurodevelopmental outcome among PPHN survivors treated with NO compared with those treated with conventional therapies.[20]

The premature newborns-uncertainties about use of INO.[21]

In the preterm neonate, severe respiratory failure is, in large part, the result of surfactant deficiency. Although treatment with exogenous surfactant can cause dramatic improvements in oxygenation. Some have suboptimal responses. Low dose INO causes immediate improvement in oxygenation in preterms.[22] It may be effective as a lung specific anti-inflammatory therapy to decrease lung neutrophil accumulation and the associated inflammatory injury and subsequent decreased incidence of chronic lung disease. INO is shown to impair platelet function in vitro, but clinical trials have not shown increased incidence of ICH,[23] and a trend in the reduced risk and severity of chronic lung disease among INO treated prematures is the main working hypothesis for most of the ongoing trials.[24]

INO in Chronic Lung Disease

Long-term ambulatory use of NO via nasal canula causes decrease in PVR and improved oxygenation in adults with stable chronic obstructive pulmonary disease. Its efficacy is not proved in interstitial pulmonary fibrosis, although transient improvement occurs. It can cause bronchodilation, but not as effectively as beta agonists.[25]

INO Therapy in Children with ARDS

The management of ARDS continues to be a challenge. Clinically ARDS is characterized by pulmonary hypertension and profound hypoxemia, abnormal vasoreactivity and increased permeability. Unlike PPHN extrapulmonary shunt does not occur in ARDS and hypoxemia is primarily due to intrapulmonary shunt (perfusion of lung units that lack ventilation). When pulmonary hypertension in ARDS is profound, right ventricular contractility may be depressed and its subsequent dilation may interfere with left ventricular function which further aggravates gas exchange.[26]

Physiological Effects of INO in ARDS (Fig. 43.4)

1. INO lowers pulmonary artery pressure and pulmonary vascular resistance.
2. Decreases V/Q mismatch-The low dose INO redirects blood flow from poorly aerated, atelectatic or diseased lung regions to better aerated distal air spaces. This is known as "microselective effects". This response is dose related, lower doses achieving greater oxygenation. At higher doses this microselective effect is lost and NO may reach poorly ventilated lung areas.[27]
3. INO decreases lung inflammation, vascular permeability and thrombosis, thus reduces permeability edema formation, although some studies suggest that it can inactivate surfactant.[26,27]
4. Permissive hypercapnea (a strategy used in management of ARDS as an attempt to decrease ventilator induced lung injury caused by barotrauma or volutrauma. Tidal volume and minute ventilation are decreased and $PaCO_2$ allowed to rise. Hypercapnea exacerbates pulmonary vasoconstriction. INO attenuates this and allows use of permissive hypercapnea.[28]

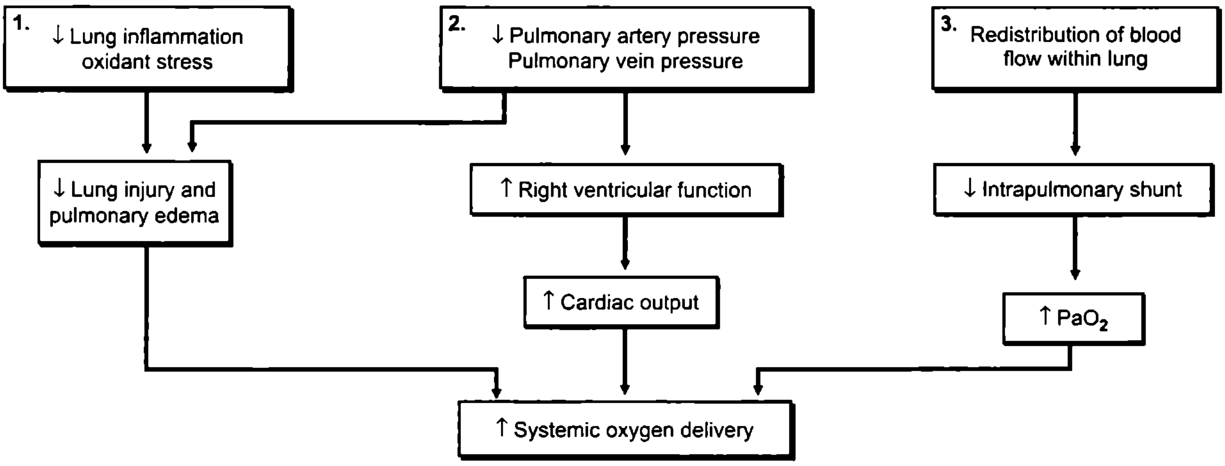
1. ↓ Lung inflammation oxidant stress
2. ↓ Pulmonary artery pressure Pulmonary vein pressure
3. Redistribution of blood flow within lung
↓ Lung injury and pulmonary edema
↑ Right ventricular function
↓ Intrapulmonary shunt
↑ Cardiac output
↑ PaO2
↑ Systemic oxygen delivery

Fig. 43.4: Physiological targets of inhaled nitric oxide therapy in acute respiratory distress

ARDS, Controversies with INO Therapy

Despite wonderful physiologic effects, it remains unproven, whether improved oxygenation in ARDS are simply cosmetic or actually beneficial in terms of mortality.[29] Various studies report acute improvement in oxygenation but fail to alter mortality, ventilator days and other critical end points. Actually ARDS is a clinical syndrome with multiple complicating factors, such as sepsis and multiorgan dysfunction. Moses prospective controlled studies using large patient population are needed to document any outcome benefits of INO therapy in ARDS.[30]

INO in Cardiology

Pulmonary hypertension with associated right ventricular dysfunction may complicate postoperative cardiac patients despite maximal pharmacologic and ventilatory support. By reducing mean pulmonary artery pressure, INO may protect the right ventricle, while maintaining left ventricular filling by increasing pulmonary arterial blood flow.[31]

Congenital Heart Disease

The use of INO has been shown to be helpful for the assessment of pulmonary vascular reactivity in selecting patients for surgery and postoperative management.[32] Post-cardiac surgery pulmonary has been successfully treated with INO in patients with significant prospective pulmonary hypertension.

Primary Pulmonary Hypertension

INO is used to test pulmonary vascular reactivity. A positive response with decrease in pulmonary artery pressure suggests a favorable response to long-term vasodilator therapy with prostacyclin or calcium channel blockers.

Miscellaneous Uses and Ongoing Trials

1. *Life-threatening status asthmaticus:* In children with life-threatening asthma, hypercapnea increases pulmonary vascular tone, thus increasing right ventricular afterload, which is already compromised by positive pressure ventilation and air trapping. NO plays an important role in regulating bronchial smooth muscle tone. Selective vasodilation of ventilated lung units may improve oxygenation and carbon dioxide elimination and unload the right ventricle, improving cardiac output.[33]
2. *Cerebral malaria:* Some researchers have used it, but prospective multicenter trials and are needed to document beneficial effects.[34]
3. *Heart transplantation:* INO is a useful adjunct to the postoperative treatment protocol of heart transplant patients with pulmonary hypertension. It selectively reduces PVR and enhances right ventricular stroke work.[35]
4. *Lung transplantation:* Reperfusion injury is a major cause of mortality and morbidity among lung transplant recipients. Prophylactic INO does not prevent reperfusion injury in human lung transplantation however, if started at reperfusion, improves gas exchange and reduces pulmonary artery pressure in those patients who develop reperfusion injury.[36]
5. *Acute myocardial infarction (AMI):* Given the important role that NO plays in regulatory platelet activation, interest has arisen in developing technique for increasing NO donors in the setting of AMI.[37]
6. *Neonatal chronic lung disease:* Defined as the continuing need in preterm infants for supplemental inspired oxygen at 36 weeks postconceptional age. INO improves oxygenation in most infants with early chronic lung disease, without inducing changes in markers of inflammatory or oxidative injury.[38]

Adverse Effects of INO

1. *Rebound effects:* Abrupt withdrawal of nitric oxide can cause rebound pulmonary hypertension, right ventricular failure and severe hypoxemia.[39]
2. *Prolonged bleeding time:* INO increases platelet cyclic GMP and by inhibiting platelet aggregation can increase bleeding time. Although clinically significant bleeding is fortunately not observed.[40]
3. *Paradoxical worsening* of oxygenation in chronic lung disease.[41]
4. *Elevated pulmonary capillary wedge pressure:* In patients with left ventricular dysfunction and poor ventricular compliance, an increase in

pulmonary flow can increase left ventricular filing pressure, leading to ventricular failure and pulmonary edema.[42]

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CHAPTER

Neonatal Ventilation

Anjali A Kulkarn

Respiratory distress is one of the commonest causes of mortality and morbidity in the neonatal period. Fortunately most of the conditions leading to respiratory failure in the newborn are reversible and complete recovery can be achieved with prompt management. Thus, adequate support of respiration is integral to the care of the sick newborn and the advent of assisted ventilation has made this possible.

Definition

Assisted ventilation is defined as the movement of gas into and out of lung by an external source connected directly to the patient.[1]

In the neonate assisted ventilation is usually a temporary measure for supporting pulmonary function until the patient can breathe adequately without help. The purpose of ventilation is to provide adequate oxygen, remove carbon dioxide and reduce the work of breathing. This is accomplished through the use of a device that augments or replaces the bellows action of the respiratory musculature.

Beneficial effects of ventilatory therapy are dependent on a strong knowledge of this subject, skill and experience in management combined with constant vigilance by medical, nursing and respiratory personnel during treatment.

Until the 1970's ventilators used in Neonatal Intensive Care Units (NICU) were modifications of adult devices. From 1971-1995 myriad of new ventilators specifically designed for neonates were manufactured and used. The first generation ventilators included the BABY bird 1, the Bournes BP 200 and a volume ventilator, Bournes LS 104/50. All operated on the intermittent mandatory ventilation (IMV) principle.

Subsequently second and third generation ventilators have allowed new dimensions in neonata assisted ventilation. This combined with development of surfactant replacement therapy has revolutionized the management of acute respiratory distress in the newborn. However, the goal of the future is the application of effective therapy without iotrogenic consequences.

It is not possible to cover the details of various ventilatory techniques however, some of the common methods, their indications, contraindications and long term effects are described in this chapter.

Initiation of Ventilation

The commonest indication for neonatal ventilation is respiratory failure. The causes of neonata respiratory failure are depicted in Table 44.1.

These can be roughly divided into two types. One where lungs are normal but patient fails to breathe i.e. apnea and second where mechanism o pulmonary gas exchange is compromised due to lung disease.

It is important to make distinction between two types of lung diseases—atelectatic and obstructive This distinction is important as it helps the clinician to address the criteria for initiation of ventilation, the choice of ventilator and the parameters of ventilator control. The specific objectives to achieve and complications to avoid in assisted ventilation of the newborn are given in Table 44.2.

The diagnosis of respiratory failure is based on clinical findings and results of acid-base analysis.

Table 44.1: Causes of respiratory failure

Problem area	Possible causes
Pulmonary	RDS, Aspiration syndromes, Pneumonia, Pulmonary Hemorrhage, Wilson-Mikity syndrome, Bronchopulmonary dysplasia, Insufficiency of prematurity, Pneumothorax, Tumor, Diaphragmatic hernia, Chylothorax, Congenital malformation
Airway	Laryngomalacia, Choanal Atresia, Pierre Robin syndrome, Micrognathia, Nasopharyngeal tumor, Subglottic stenosis
Abnormalities of muscles of respiration	phrenic nerve palsy, Spinal cord injury, Myasthenia gravis, Werdnig-hoffmann syndrome
Central problems	Apnea of prematurity Drugs: Morphine, magnesium sulphate, mepivacaine, meperidine, Seizures Birth asphyxia, Hypoxic encephalopathy, Intracranial hemorrhage, Ondines curse, Rapid eye movement sleep
Miscellaneous	Congestive heart failure, Persistent fetal circulation, Postoperative anesthesia/Sedation, Tetanus neonatorum, Extreme immaturity, Shock, Sepsis, Hypoglycemia, Electrolyte abnormalities, Acid-base imbalance, Infant botulism Hydrops fetalis

1. Clinical manifestations
   - Increasing respiratory rate
   - Increasing respiratory effort/retractions
   - Prolonged apnea, cyanosis not relieved by oxygen administration
   - Gasping and use of accessory muscles of respiration

   Silverman Anderson score is often helpful in evaluation and score of > 7 indicates impending respiratory failure.
2. Blood gas parameters
   - $PaO_2 < 50$ mmHg
   - $PaCO_2 > 60$ mmHg
   - Ph < 7.25.

Basic Principles of Ventilation

According to classic theory, ventilation involves the movement of gas by convection or bulk flow through the conducting airways and then by molecular diffusion into the alveoli and pulmonary capillaries. The driving force for convection is the difference in pressure at origin and distension of the flowing gases, for diffusion it is the difference in the concentration of the intermingling gases in the adjacent spaces.

The amount of gas drawn in through the nose on delivered breath during a single cycle of ventilation is called tidal volume (VT). VT in milliliters multiplied by the number of breaths per minute or respiratory frequency defines minute ventilation (VE).

$$VE = VT \times f$$

Table 44.2: Objectives of ventilation

Objectives to achieve	Complications to avoid
Maintain desired level of PaO_2 or SaO_2	Avoid O_2 toxicity to the lungs, bronchopulmonary dysplasia, Retinopathy of prematurity, Hypoxemia pulmonary vasoconstriction or tissue damage
Maintain desired level of $PaCO_2$ optimum level of alveolar ventilation	Avoid Hyperventilation causing cerebral ischemia,
Reduce work of breathing and respiratory muscle fatigue	Avoid alveolar overdistension, wasted ventilation, rupture and pulmonary air leak Suppression of ventilatory drive Increased upper airway resistance
Re-expand atelectatic or collapsed alveoli and lung segments	Hyperinflation/overexpansion of areas already inflated Pulmonary hypoperfusion, Reduced venous return and cardiac output

The trailing portion of the column of incoming tidal gas never arrives at the alveoli but rather fills the conducting airways. This portion constitutes the anatomic deadspace. Another portion of the tidal gas may be delivered to the alveoli but may enter the alveoli that are not perfused. Since gas exchange does not take place in these units the volume that they constitute is called alveolar deadspace. Together they are called total or physiologic deadspace (VDS). The ratio of deadspace to tidal volume defines wasted ventilation which reflects the proportion of tidal gas delivered that is not involved in actual gas exchange.

Types of Ventilatory Support

Continuous Positive Airway Pressure (CPAP)

A continuous flow of heated humidified gas is circulated past the infants airway at a set pressure of 3-8 cm of H_2O maintaining an elevated end expiratory lung volume while the infant breathes spontaneously. CPAP is usually delivered by means of nasal prongs or nasopharyngeal tube. It improves oxygenation by an increase in the functional residual capacity. However, over reliance on CPAP may be dangerous and it should only be used if infants show adequate respiratory effort, appear to be tolerating the procedure well and maintain adequate arterial blood ($pCO_2 < 50$ mmHg, pH > 7.25, $PaO_2 > 50$).

With all CPAP devices some air may get into the gut and cause gastric distension. This can be prevented by using an open ended oro-gastric tube *in situ*. CPAP effectively splints the chest wall, keeps the airways patent thereby preventing obstructive apnea and atelectasis. Various studies have documented the efficacy of CPAP in respiratory distress of mild to moderate degree.[2] Recently trials have been conducted on using nasal intermittent positive pressure (NIPPV) and it has been found to have similar results as CPAP. Indigenous CPAP systems as well as CPAP machine may be used to deliver CPAP. However, a facility for ventilation should be available in case the patient has deterioration in respiratory status.

Conventional Ventilation

Conventional ventilators can be classified in different ways as given below:

1. By pressure relationship to patient, i.e. positive or negative.
2. By cycling mode (at termination of inspiration).
3. By power source.
4. By rate.

The commonest type of ventilation used for neonates is pressure limited, time cycled ventilation where a peak inspiratory pressure is set and gas is delivered to achieve that target pressure.

After the target is reached, the remainder of the gas volume is released into the atmosphere as a result *the tidal volume delivery with each breath is variable* despite the recorded peak pressure being constant.

Inspiration also ends after a preset time period.

In contrast, in volume limited modes, a preset volume is delivered with each breath regardless of the pressure that is needed.

Some ventilators also use airway flow as the basis of cycling in which inspiration ends when flow has reached a critical low or preset level (flow cycled ventilation).

In pressure limited, time cycled continuous flow ventilators following parameters are set at the outset:

- Peak inspiratory pressure (PIP).
- Peak end expiratory pressure (PEEP).
- Inspiratory time (ti).
- Rate.

This system is relatively simple and maintains good control over respiratory pressures.

Disadvantages

- Poorly controlled tidal volume.
- Does not respond to changes in respiratory compliance.
- Spontaneously breathing infants may receive inadequate ventilation and are at increased risk for airleaks.

Alternative Modes of Ventilation

Due to disadvantages associated with conventional ventilation, the following alternative strategies are being used increasingly.

Patient Triggered Ventilation (PTV)

This is a form of ventilation where machine-delivered breath is initiated in response to a signal derived from the patient's own inspiratory effort, thus synchronizing the onset of both spontaneous and mechanica breaths. The types of signals used to provide PTV to newborn vary and could be impedance, pressure or flow. The basic feature is shifting the control of breathing from clinician to patient and the newer generation of ventilators allow its application to the smallest of babies.[3]

PTV can be of following types.

a. *Assist/control ventilation* This is the best mode of ventilation in acute phase of illness as it requires least amount of patient effort and produces improved oxygenation at the same or lower mean airway pressure than conventional modes. In this type of ventilation a positive pressure breath is delivered in response to patient's inspiratory effort (assist) provided it exceeds a preset threshold criteria. There is a back-up rate (control) in case patient stops breathing. The inspiratory flow is proportional to patient effort and ventilation is tolerated well.
b. *Synchronous intermittent mandatory ventilation (SIMV)* In this mode of ventilation mechanically delivered breaths are cycled at a rate set by the clinician but are synchronized to the onset of the patient's own breath. Patient breathes freely inbetween the mechanical breaths. This insures less risk of 'fighting' or airleaks and sedation is not required. SIMV is particularly helpful for weaning from ventilation.[4]
c. *Pressure support ventilation (PSV)* This is similar to assist/control ventilation except that it is flow cycled, thus patient has full control over how much to breathe and for how long (ti). Although PSV can be used for full ventilation (PSV max), in practice it is generally used as a weaning mode.
d. *Proportional assist ventilation (PAV).*
e. *Mandatory minute ventilation (MMV).*

There are other promising ventilatory strategies currently under development for clinical use but no data is available relating to their use in neonates.

Rescue Strategies for Management of Ventilatory Failure

Despite improved ventilatory technique, conventional ventilation may fail in certain situations. A commonly used parameter to assess the efficacy of ventilation is oxygenation index (OI).

$$OI = P_{AW} \times FiO_2 \times 100\ PaO_2$$

P_{AW} = mean airway pressure
FiO_2 = concentration of inspired oxygen
PaO_2 = partial pressure of oxygen

OI of 25-40 indicates insufficient ventilation with existing mode of support.

OI of > 40 indicates respiratory failure.

Various rescue therapies, as given below, are currently practiced.

High Frequency Ventilation

This can be of two types–High Frequency Oscillatory Ventilation (HFOV) and High Frequency Jet Ventilation (HFJV) (see chapter on High Frequency Ventilation).

In newborns high frequency oscillation has been found to be effective in certain situations. During this type of ventilation a continuous flow of fresh gas rushes past the source that generates the oscillation and a controlled leak or low pass filter allows the gas to exit the system. Both inspiration and expiration are active processes. Oscillations are generated at a frequency ranging from 3 HZ-15 HZ [1 hertz (HZ) = 60 breaths] per minute. Pressure oscillations within the airway produce tiny tidal volume fluctuations around a constant distending pressure. The amplitude of the pressure, which varies from 15-50 cm H_2O, determines the tidal volume. This ventilation causes uniform recruitment of alveoli and there is significantly lower risk of air leaks.

Earlier studies on HFOV had raised some doubts about the risk of IVH, however randomized controlled trials carried out with proper selection criteria have depicted a significantly better outcome with HFOV in certain conditions.[5] This mode of ventilation has been found to be effective in respiratory distress complicated by PPHN (primary pulmonary hypertension).[6] Only Sensorimedics 3100/3100A, a high frequency oscillator has been approved by FDA for early intervention (prophylactic HFOV) but it is not commonly preferred form of therapy.

High Frequency Jet Ventilation is a variant of HFOV and the differences are tabulated in Table 44.3.

Inhaled Nitric Oxide (INO)

(Please Refer to Chapter on Nitric Oxide).

Nitric oxide (NO) appears to be ubiquitously distributed within universe. Critical care physicians

Table 44.3: Differences in high frequency jet ventilation (HFJV) and high frequency oscillatory ventilation (HFOV)

	[illegible]	[illegible]
Rate (HZ)	1.5-3.00	3.00-15
Expiration	PASSIVE	ACTIVE
Special ETT (reintubation)	YES	NO
Gas Exchange	++	++
$PaCO_2$ reduction	++	++
PaO_2 increase	+ –	+
Cardiac output	+ –	–
Tracheal injury	++	?

have been most interested in the profound regulatory effects of NO on vascular tone. Inhaled nitric oxide distributes only to aerated lung where it rapidly diffuses from endothelial cells into subjacent vascular smooth muscle cells and stimulates Guanylate Cyclase to increase the concentration of Cyclic Guanosine Monophosphate (GMP) that in turn causes smooth muscle relaxation. This localized vasodilator effect improves V/Q mismatch. NO that diffuses into vascular space is quickly converted to methemoglobin thereby avoiding systemic vasodilator effect. Inhaled nitric oxide is particularly useful for treating persistent pulmo-nary hypertension complicating RDS.[7] This can be used with both conventional and high frequency ventilation. Kinsella *et al* have reported outcome in nine cases of PPHN treated with INO. Within 15 minutes of initiation, PaO_2 increased from 55 mm Hg to 136 mmHg and OI reduced from 60 to 26.[8] The first three had to be shifted to ECMO but the remaining six recovered completely.

Patients with pulmonary hypertension secondary to congenital heart disease may also benefit both diagnostically and therapeutically from NO. Sometimes NO may combine with O_2 to form NO_2 and peroxynitrite, which could be highly toxic to the body. Thus, further studies are required to confirm the short-term and long-term safety of INO usage in very young infants. The dose range used (10-80 parts per million) also needs to be standardized, lower end of dose (10-20 ppm) seems to be as effective. It is prohibitively expensive therapy.

Extracorporeal Membrane Oxygenation (ECMO)

This is a life-support technique used for profound cardiorespiratory failure in infants who fail to respond to conventional therapy.[9] The need for ECMO has declined after the arrival of HFOV and INO for treatment of persistent Pulmonary hypertension.

Method

Extracorporeal life-support is provided by draining blood from venous circulation, adding oxygen, removing carbon dioxide via membrane oxygenator (artificial lung). Blood is returned to either the venous or arterial circulation. ECMO allows "lung rest" and lungs are protected from further injury due to barotrauma or oxygen since lower ventilatory settings can be used.

Indications

1. Reversible respiratory failure.
2. Predicted mortality rate with conventional therapy great enough to warrant the risk of ECMO.
3. Oxygenation index of greater than 40 with 2 hours of conventional ventilation. This treatment is available at few centers across the globe.

Contraindications

Absolute

1. Greater than grade III IVH.
2. Two or more weeks of mechanical ventilation.

Relative

1. Greater than grade II IVH.
2. Birth weight < 2 kg or gestation < 34 weeks.
3. Mechanical ventilation for more than 10 days.

Liquid Ventilation (LV)

The principle behind LV is based on laplace equation — $P = 2\,T/r$

P — distending alveolar pressure

T — surface tension

r — radius of alveolus

This indicates that if surface tension is decreased, lung expansion can be accomplished more easily and even small alveoli can be maintained open for gas exchange at low distending pressures.

Two forms of LV currently exist:

- TLV (Total liquid ventilation)
- PLV (Partial liquid ventilation) or PAGE (Perfluro-carbon associated gas exchange)

In TLV a volume of perflurocarbon equal to lungs FRC is instilled via an Endotracheal tube and tidal volume (VT) aliquots of liquid are subsequently cycled to effect gas exchange, often utilizing highly specialized apparatus. In PAGE a volume of perflurocarbon equal to lungs FRC is instilled via ETT but the subsequent tidal ventilation is performed with respiratory gas administered via a standard mechanical ventilator at conventional sittings.

Greenspan *et al* were the first to report the clinical application of a liquid breathing technique.[10] They treated 3 premature infants with HMD who failed to respond to conventional ventilation, using TLV by a gravity flow devise. Therapy was limited to 2 cycles each of 5 minutes followed by regular gas ventilation. All patients showed marked improvement in compliance and oxygenation without any signs of homodynamic instability. This can be further improved with PLV as the high resistive component that contributes to increased airway pressure with TLV is largely obliviated.

However, Dose-response curves for various applications of LV need to be determined and new perflurocarbons developed the physical properties of which will facilitate particular therapies. This type of ventilation is still experimental in nature and further study is indicated to asses long-term perflurocarbon toxicity particularly for application in preterm infants.

Supportive Therapy with Mechanical Ventilation

Sedation—Sedation is generally required to limit the distress and agitation associated with intubation and ventilation. Morphine infusion (0.1-0.2 mg/kg/hr) is generally used for this purpose. Other drugs like midazolam are sometimes added.

Muscle relaxation—Infants who continue to fight ventilation, particularly bigger/term babies and babies with PPHN are paralyzed using boluses of pancuronium to have effective ventilation. Prolonged muscle relaxation leads to fluid retention and reduction in compliance.

Blood gas monitoring—All neonates on ventilation require continuous monitoring of oxygen saturation and acid base status.

Complications and Sequelae

A. Mechanical
   1. ET obstruction-atelectasis
   2. Equipment malfunction
B. Barotrauma and oxygen toxicity (BPD)
C. Air leak syndrome
D. Complication of invasive monitoring
   1. Peripheral arterial occlusion –infarction
   2. Aortic thrombosis
   3. Embolization
E. Anatomic
   1. Subglottic stenosis
   2. Palatal grooves
   3. Vocal cord damage

Assessing the Outcome

It is important for a unit that offers ventilation to newborns to assess the outcome from time to time. Over the years respiratory failure as a cause of mortality has come lower in order following intraventricular hemorrhage and sepsis. Regular statistical reviews should be performed to see the outcome of very low birth weight babies. In Indian setup we can offer ventilation and surfactant therapy to babies more than 26 weeks gestation and more than 600 Gms birth weight, but in smaller babies outcome may not be very good. It is therefore recommended that every NICU should weight the benefit of neonatal ventilation as per their outcome and make judicious use of technology.

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CHAPTER

Surfactant Therapy in the Newborn

Vidya Gupta

Surfactant replacement therapy has been shown to be an effective treatment for premature newborns with hyaline membrane disease. Survival of the very preterm neonate has improved enormously with the use of exogenous surfactant. In the pre-surfactant era preterm survival was as low as 40-50 percent. This has increased to near 90 percent even in the very low birth weight babies following surfactant use. Overall improved neonatal care also contributes to the decrease in neonatal mortality and morbidity.

Surfactant deficiency was recognized as the cause of preterm RDS as early as 1949, yet it was a long time before surfactant was effectively used. Early attempts to provide surfactant replacement by Robilland *et al* in 1964 and Chee *et al* in 1967 were unsuccessful. In 1973 Robert and Euhorning directly instilled surfactant through a tracheostomy into the upper airway in rabbits. The first successful reports of human trials came from Fujiwara *et al* in 1980. Bovine lung saturated phosphatidyl choline and other lipids were used.

Surfactant Composition

Surfactant is produced by the type 2 alveolar cells in the lung. Mammalian surfactant contains 70-80 percent phospholipids; 10 percent protein and 10 percent natural lipids, primarily cholesterol. The predominant phospholipid is phosphatidyl choline which exists in both the saturated and unsaturated forms. The larger proportion, saturated phosphatidyl choline, is the principal surface-active component of surfactant and is also known as dipalmitoyl phosphatidyl choline (DPPC). DPPC is the component that decreases surface tension at the air water interface in the alveolus to close to zero. The unsaturated phosphatidyl choline and surfactant proteins facilitate the absorption of DPPC. The composition of Surfactant is depicted in Figure 45.1.

Surfactant proteins (SP) are identified as Protein A, B, C and D.[1] SPB and C are the hydrophobic proteins. Surfactant protein A and D are known as hydrophilic proteins. SPB and SPC promote surface absorption of DPPC. Genetic SP-B deficiency causes death due to a severe RDS like syndrome soon after birth. In this case Surfactant treatment is not effective as there are no path-ways for reprocessing and secreting surfactant. SPB is responsible for processing SPC to its active peptide. SP-B, SP-C and lipids interact *in vivo* to provide the essential biophysical properties of surfactant. SP-A and D contribute to host defense by binding a wide range of gram positive and

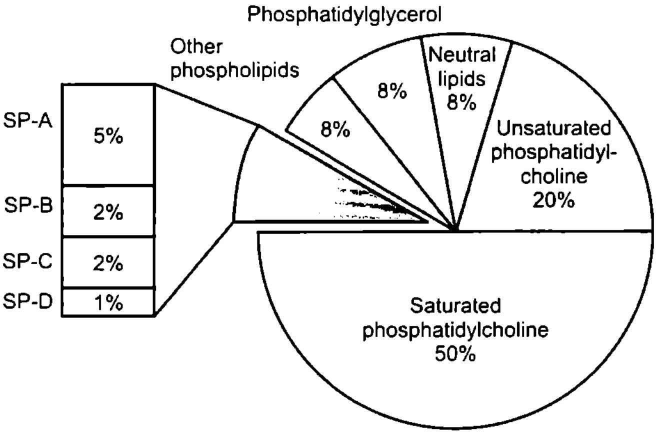


Fig. 45.1: Composition of surfactant

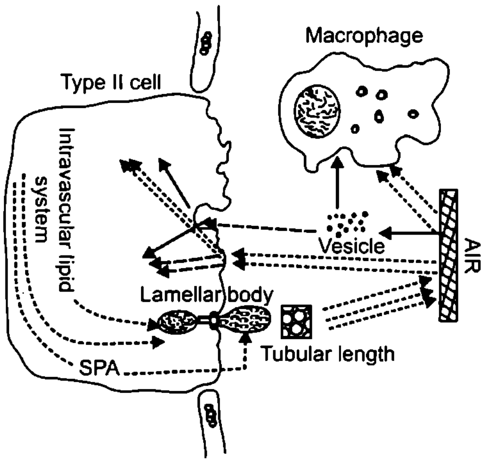


Fig. 45.2: Surfactant metabolism

gram negative microorganism, aggregating viruses, promoting opsonization and phagocytosis. Surfactant metabolism is depicted in Figure 45.2.

Surfactant Synthesis and Function

DPPC is synthesized in the endoplasmic reticulum and transferred to lamellar bodies along with the proteins SP-B and SP-C. The lamellar bodies are the storage and secretory granules for surfactant. These are contained within a limiting membrane that fuses with the plasma membrane during secretion. Once secreted to the hypo phase the lamellar bodies unravel to form tubular myclin that absorbs rapidly to produce a lowering of surface tension.

At birth in a term infant the amount of alveolar surfactant is actually 10 fold higher than in an adult lung, but the time from synthesis to secretion is slower in the preterm and term lung as compared to adults. Once surfactant is secreted the turnover time is longer in the neonate. 90 percent of DPPC is recycled into the type 2 cells for resecretion. Cortisol administered antenatally to the mother induces foetal lung maturation by increasing surfactant production.

Acute lung injury results in a decrease in the amount of the surface-active forms of surfactant and an increase in the amount of the vesicular or catabolic forms which have poor biophysical function. Alveolar ocdema usually follows acute lung injury; the presence of plasma protein and blood products in the alveolus decreases surfactant availability and surfactant activity. The altered surfactant activity results in a loss of compliance, as well as a loss of lung gas volume, increased atelectasis and more ventilation perfusion mismatch.

Surfactant therapy results in a decrease in the opening pressure of the alveolus, more uniform alveolar inflation, and less over distension. The use of PEEP between 4-7 cm H_2O helps to preserve surfactant function.[2]

Types of Surfactants

Surfactant for clinical use may be "natural" (derived from animal sources) or "synthetic" (artificially produced).

Natural surfactant is obtained from either bovine or Porcine lungs, which is purified and includes extraction with organic solvents. This removes the hydrophilic proteins SPA and SPD, leaving a material containing only lipids along with small amounts of SPB and SPC.

Synthetic surfactant does not contain any surfactant proteins. It contains approximately 85 percent Phospholipids-DPPC along with spreading agents like hexadecanol and tyloxapol. Recent research has focused on adding a surfactant protein like substance to improve the activity of synthetic surfactant. Two synthetic surfactants are currently undergoing trial–'surfaxin' which contains the KL4 peptide which mimics SPB and 'venticute' containing a recombinant form of SPC.

Natural and synthetic surfactants are listed in Tables 45.1 and 45.2.

Surfactant therapy results in rapid improvement in oxygenation. Inspiratory pressure and oxygen concentration can often be decreased fairly rapidly. This is accompanied by an increase in the functional residual capacity, an increase in lung compliance, and a decrease in the ventilation perfusion mismatch. Functional residual capacity increases due to improved deflation stability and a longer expiratory time constant.

In addition to the cardiopulmonary changes, treatment with exogenous surfactant also results in radiological improvement. The typical X-ray appearance of RDS with an air bronchogram disappears following surfactant therapy. The clearing of the lung fields seen may be uniform, patchy or

Table 45.1: Natural surfactants

Trade name	*Protein and major * phospholipid content*	*Manufacturer*
Surfacten	DPPC, PG, SP-B, SP-C	Tokyo Tanabe (Japan)
Survanta	DPPC, PG, SP-B, SP-C	Ross Products Division of Abbott Laboratories (USA)
Curosurf	DPPC, SP-B, SP-C	Chiesi Pharmaceuticals (Italy)
Infasurf	DPPC, SP-B, SP-C	Forest Laboratories (USA)
BLES	DPPC, SP-B, SP-C	BLES Biochemicals (Canada)
Alveofact	DPPC, SP-B, SP-C	Boechringer Ingelheim (Germany)

*All natural surfactants contain smaller proportions of other Phospholipids, neutral lipids and fatty acids. The purification processes using organic acids remove hydrophilic proteins. Hence, none of the natural surfactants contain either surfactant protein A (SP-A) or surfactant protein D (SP-D).

Table 45.2: Synthetic surfactants

Trade name	*Protein and major * phospholipid content*	*Manufacturer*
Exocurf	DPPC, no protein	Burroughs-Wellcome Company (USA and UK)
Pneumactant*	DPPC and PG, no protein	Britannia Pharmaceuticals (UK)
Surfaxin	Sinapultide, DPPC, POPG and palmitic acid	Discovery Laboratories (USA)
Venticute	RSP-C, DPPC, POPG and palmitic acid	Byk Gulden (Germany)

*Pneumactant was removed from the market by the manufacturer in the year 2000.

asymmetric, sometimes with a disproportionate improvement of the radiological changes in the right lung.[3,4]

Evidence for Surfactant

Many randomized controlled trials have been conducted in newborns to assess different aspects of surfactant therapy. The finding from these trials have been grouped according to the questions the trials have addressed. These have been reviewed in multiple systematic reviews in the Cochran database of systematic reviews.

Surfactant Therapy Compared with Placebo or No Therapy

Many of the trials in the early 1980's studied the effect of surfactant compared with placebo or no therapy. Surfactant was administered prophylactically in some of these trials and as rescue in others. Different preparations of both natural and synthetic surfactants were used. Systematic reviews of these trials reveal that compared with placebo or no therapy, surfactant treatment decreases the risk of pneumothorax and decreases mortality. Estimate from the meta-analysis indicate that there is a 30-65 percent relative reduction in the risk of pneumothorax and upto a 40 percent relative reduction in the risk of mortality.

Natural vs Synthetic Surfactants

Both natural and synthetic surfactants are effective. Natural surfactants have a more rapid onset of action allowing a rapid lowering of both FiO_2 and inspiratory pressure. Onset of action with synthetic surfactant is less rapid and the improvement is less dramatic. A meta-analysis of the trials of natural vs synthetic surfactant indicate that treatment with natural surfactant extracts resulted in a decreased frequency of pneumothorax and a decreased mortality. There was no significant differences in chronic lung disease, intraventicular hemorrhage sepsis, or patent ductus artenosus.[5-7]

Comparison of Different Types of Natural Surfactants

Using the same dose (mg/kg) of natural surfactant, there is no evidence that one preparation is superior to the others. Individual user familiarity and expertise with a particular preparation may result in one product being apparently superior to another.[8]

Prophylactic Surfactant Administration vs Rescue Administration

Even 15-30 min periods of ventilation before surfactant administration have been shown in animal models to cause acute lung injury.[9-11] This appears to be the rationale for the early use of surfactant. Babies less than 1000gms and or less than 28 weeks gestation are often treated with prophylactic surfactant.

Prophylactic therapy in the true sense means surfactant administration before the first breath. This often interferes with resuscitation immediately after birth. By using prophylactic surfactant, however, a certain number of babies will need to be intubated and treated unnecessarily. At what point the potential benefits of prophylactic surfactant outweight the costs and problems associated with unnecessary ventilation needs to be decided and is under research.

Early vs Late Rescue Therapy

Surfactant may be administered as rescue therapy, early, at 30 min. to two hours of age when the first signs of RDS are apparent or late, at or after 2 hours of age after RDS is well established. The largest randomized surfactant trial conducted in neonatology, the OSIRIS trial, evaluated early vs delayed selective surfactant administration.[12,13] Early administration consisted of the administration of the first dose of surfactant with in the first two hours of the life. The results of this trial as well as the meta-analysis of other randomized control trials looking at this show a decrease in the risk of pneumothorax, pulmonary interstitial emphysema, chronic lung disease and neonatal mortality.

Often more than one dose of surfactant is needed. The use of more than one dose has been associated with an improved outcome. An oxygen requirement of FiO_2 >0.30 or persistent or worsening signs of RDS are used as criteria for treatment with further doses of surfactant.

Adverse effects of surfactant therapy include transient hypoxia and bradycardia as a result of acute tube obstruction after administration. Other adverse effects include reflux of the drug into the pharynx, hypercarbia, hypotension, decreased cerebral blood flow velocity, and pulmonary hemorrhage. The occurrence of pulmonary hemorrhage may be related to the presence of a patent ductus arteriosus.

Methods of Administration of Surfactant (Flow chart 45.1)

Surfactant has to be instilled into an endotracheal tube. It cannot be effectively delivered by nebulization.

Once a preterm baby is delivered it is observed for evidence of respiratory distress. Once respiratory distress is documented, and the oxygen requirement increases to 40 percent or more, the baby is intubated. The tube position has to confirmed radiologically before surfactant is instilled. The lower end of the ET tube must be above the carina, ideally in the mid tracheal position. Once the position is confirmed surfactant is instilled down the tube.

Different manufacturers have different instructions for surfactant instillation. It is always best to follow the technique recommended. The surfactant may be instilled via a side port on the ET tube adaptor as with Exocerf, or it may be instilled via a catheter inserted into the ET tube as in the case of Survanta. Unlike the side port technique, this results in a brief period of interruption of ventilation. Surfactant has been instilled down a dual lumen endotracheal tube by some workers and this perhaps is the technique that results in minimal interference with ventilation.[14] It has been shown that a rapid (2 min.) instillation of surfactant results in more uniform dispersal and more effective therapy. Slow delivery of the drug (20 min.) by infusion with a syringe pump results in uneven distribution.[15,16] Aerosolization or nebulization has been shown to be relatively ineffective. Spread of surfactant is essentially gravity dependent and although some manufacturers recommend changing position during therapy, there is no evidence that this results in more even dispersal. *In utero* administration has also been described, but has not been found to be effective.

It is important to remember that endotracheal suction must be avoided following surfactant therapy for at least 2 hours (Flow chart 45.1).

In the long-term outcome studies there is evidence that more infants survive after surfactant therapy, and that they are at no selective disadvantage for neuro developmental sequelae because of the surfactant therapy. Some studies have reported a lower frequency of subsequent clinical respiratory disorders in surfactant treated infants whereas others have reported no difference. In contrast some have reported an increase in allergic manifestation. No significant differences in weight or height outcome have been reported between surfactant and placebo treated infants.

There is evidence that surfactant therapy may be of benefit in numerous disorders other than RDS. These include:

- Meconium Aspiration Syndrome (MAS)
- Acute Lung Injury
- Acute Respiratory Distress Syndrome (ARDS)
- Pulmonary Hemorrhage
- Pneumonia or Sepsis
- Congenital Diaphragmatic Hernia
- Broncholitis and respiratory syncytial virus pneumonia
- Chronic Bronchitis
- Asthma
- Chronic Obstructive Pulmonary disease
- Lung transplantation
- Cystic Fibrosis
- Otitis Media

In these disorders surfactant production may be compromised as a result of injury to the type 2 alveolar cells, or existing surfactant may not be functional–that is surfactant function may be inhibited. The presence of substances like meconium, blood or protein results in the breakdown of surfactant to a smaller particle, that is biologically non-effective. The products of inflammation such as cytokines and proteases in the alveolus are responsible for disrupting surfactant and interfering with functions.

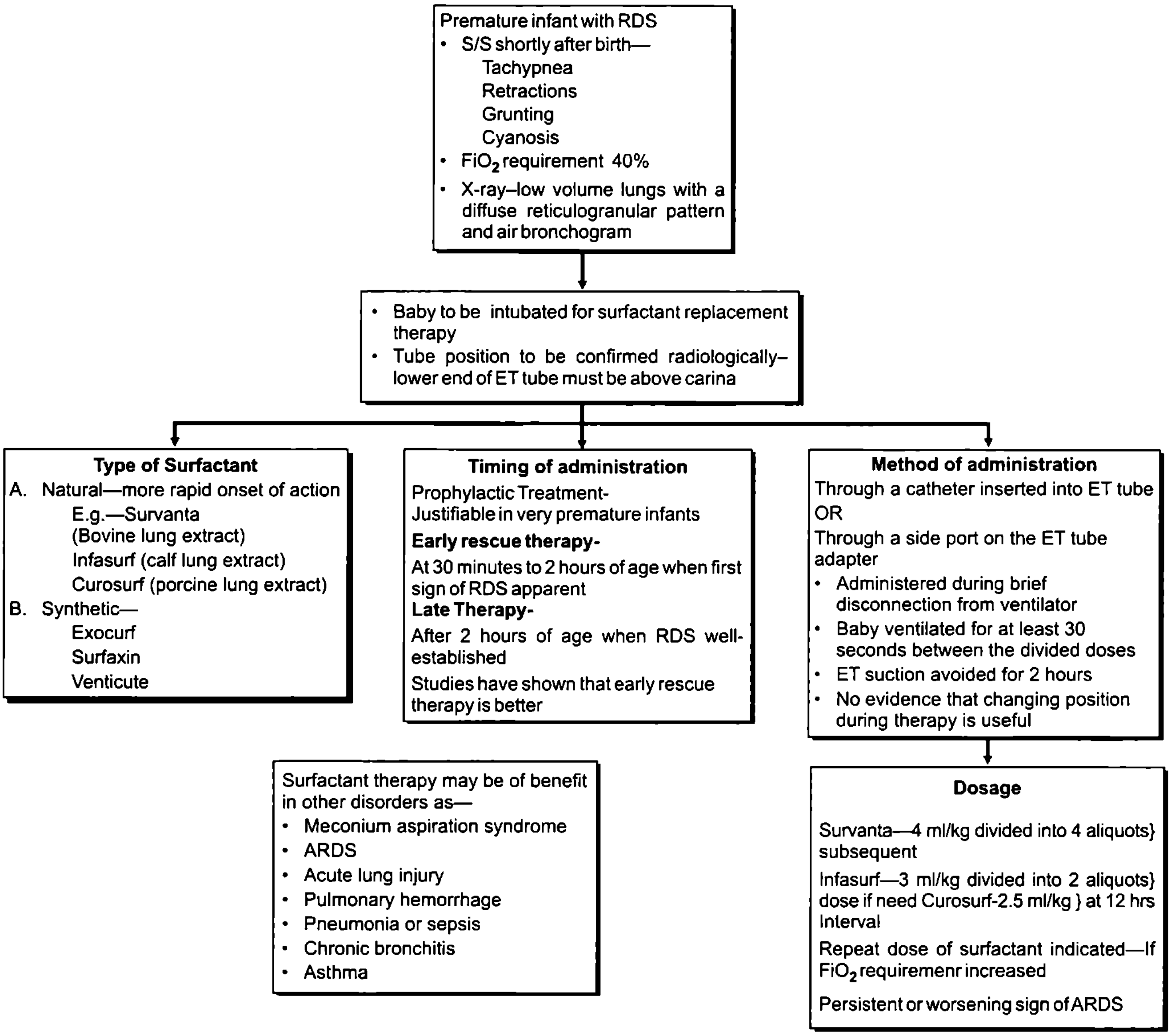
Surfactant Therapy in MAS

Relatively little clear-cut evidence exists to support the use of surfactant in disorders other than RDS. The use of surfactant in MAS has received the most attention. Small trials have been conducted using surfactant in babies with MAS and in adults with acute RDS.

Meconium Aspiration Syndrome occurs in-term babies. Meconium in this has been both swallowed and aspirated into the lung. It is known that meconium diluted to as little as in 1:6500 adversely affects surfactant function. Meconium contains proteolytic enzymes, free fatty acids, bile salts, blood and phospholipases. All these substances cause cellular injury, intense inflammation and surfactant disruption. Histologically, the picture is one of hemor-rhagic pulmonary edema. Significantly higher levels of plasma thromboxane B_2 and 6-Keto-prostaglandin $F_1 \alpha$ have been documented. These play an important role in causing vasoconstriction of pulmonary arteries contributing to persistent pulmonary hypertension seen in these babies.

In the early 1990's several anecdotal reports appeared describing the use of surfactant in MAS. Finley *et al* in 1996 described surfactant replacement in meconium aspiration syndrome. A randomized controlled trial of 40 infants with MAS was carried out and surfactant was infused over 20 min. Higher than standard doses of surfactant were used. Surfactant treated infants were less likely to have pneumothorax or require extra corporeal membrane oxygenation (ECMO) and had fewer days of mechanical ventilation, oxygen therapy and hospitalization. Lotze *et al*[17] in 1998 enrolled 328 infants with respiratory failure in a trial. Half of these had MAS as the cause of their respiratory failure. The treated infants received four standard bolus doses of bovine surfactant (100 mg/kilo). The surfactant treated infants were significantly less likely to require ECMO. There was no demonstrable difference in mortality, air leaks, duration of mechanical ventilation, oxygenation or hospitalization.

A different method of surfactant administration i.e. surfactant lavage therapy has also been described. Dilute surfactant is used as the lavage fluid. Because surfactant is a detergent. It should have a cleaning action on the lungs and meconium inflammatory cells, ocdema fluid, proteins, blood and other debris could be washed out leaving behind a layer of functional exogenous surfactant. Bovine surfactant (6 mg/ml) administered in small aliquots of (1 ml/kg) was used by Ogawa *et al*[18] in four babies with MAS. All 4 babies showed improvements. Lam and Yeung[19] also performed a similar study of 6 infants with MAS and found the lavage infants to



Flow chart 45.1: Surfactant therapy in newborn

Premature infant with RDS
- S/S shortly after birth—
  Tachypnea
  Retractions
  Grunting
  Cyanosis
- FiO_2 requirement 40%
- X-ray–low volume lungs with a diffuse reticulogranular pattern and air bronchogram

- Baby to be intubated for surfactant replacement therapy
- Tube position to be confirmed radiologically–lower end of ET tube must be above carina

Type of Surfactant

A. Natural—more rapid onset of action
  E.g.—Survanta
  (Bovine lung extract)
  Infasurf (calf lung extract)
  Curosurf (porcine lung extract)

B. Synthetic—
  Exocurf
  Surfaxin
  Venticute

Timing of administration

Prophylactic Treatment-
Justifiable in very premature infants

Early rescue therapy-
At 30 minutes to 2 hours of age when first sign of RDS apparent

Late Therapy-
After 2 hours of age when RDS well-established

Studies have shown that early rescue therapy is better

Method of administration

Through a catheter inserted into ET tube
OR
Through a side port on the ET tube adapter
- Administered during brief disconnection from ventilator
- Baby ventilated for at least 30 seconds between the divided doses
- ET suction avoided for 2 hours
- No evidence that changing position during therapy is useful

Surfactant therapy may be of benefit in other disorders as—
- Meconium aspiration syndrome
- ARDS
- Acute lung injury
- Pulmonary hemorrhage
- Pneumonia or sepsis
- Chronic bronchitis
- Asthma

Dosage

Survanta—4 ml/kg divided into 4 aliquots} subsequent

Infasurf—3 ml/kg divided into 2 aliquots} dose if need Curosurf-2.5 ml/kg } at 12 hrs Interval

Repeat dose of surfactant indicated—If FiO_2 requiremenr increased

Persistent or worsening sign of ARDS

have a more rapid improvement in oxygenation with earlier weaning from mechanical ventilation. This method needs further research.[20]

Animal trials using a combination of surfactant and various substances have been conducted. Polyethylene glycol and dextran is added to surfactant and then instilled into the trachea of the animals with meconium aspiration. This combination has been found to improve both oxygenation and compliance. Other workers have tried surfactant lavage following by liquid ventilation and also found it to be successful.

Other conditions where surfactant has been tried as a form of treatment include congenital diaphragmatic hernia, ARDS and some forms of viral pneumonia. The belief that an underlying surfactant deficiency exists along with the primary disease and forms the rationale for surfactant use.

CONCLUSION

The cumulative evidence that surfactant therapy is a benefit in RDS is overwhelming. Very few forms of therapy have been studied in as much detail and there is no doubt that the use of surfactant in RDS is a universally accepted form of treatment. However, the role of surfactant in other disorders remains controversial. There are only a few small randomized control trials supporting its use in MAS and in ARDS. The optimum doses, method of delivery and duration of treatment for non-RDS disorders is an area of further research.

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CHAPTER

46

Extracorporeal Membrane Oxygenation (ECMO)

Rohit P Rao, Ramesh Sachdeva

Through extensive research and development in the area of cardiopulmonary bypass, machine-managed extra-corporeal oxygenation of blood has greatly evolved. In 1937, the first attempt at extracorporeal oxygenation was made by the direct bubbling of oxygen gas into blood. These oxygenators caused severe hemolysis and protein denaturation, which was a result of the direct blood-gas interface. Thus, their use was limited to only a few hours.

In order to overcome this complication, use of a semipermeable membrane oxygenator was implemented. This prevented direct contact of blood and gas, and the concept of prolonged extracorporeal support was born. Clinical reports of long-term, membrane extracorporeal support of patients with respiratory failure were described in the early 1970s. By 1974, 150 adult patients with respiratory failure of diverse etiologies had undergone extracorporeal support. This led to a multicenter trial comparing extracorporeal membrane oxygenation (ECMO) vs conventional ventilation, which showed that early survival rates were unchanged. Therefore, ECMO as a treatment modality in adult respiratory failure has not gained universal popularity.

In the same period, however, neonates [especially those with persistent pulmonary hypertension of the newborn (PPHN)] had improvement in outcomes secondary to ECMO, although premature babies at less than 35 weeks gestation had an unacceptably high incidence of intracranial hemorrhage. Since then, ECMO as a rescue treatment modality for infants over 35 weeks gestation and children has grown and become increasingly popular in intensive care units.

Indications and Outcomes

The largest group of people that requires ECMO is neonates. The most common indications among them include: PPHN, meconium aspiration, respiratory distress syndrome (RDS), congenital diaphragmatic hernia, pneumonia, sepsis, and idiopathic causes. These indications and their outcomes are summarized below in Tables 46.1 to 46.4.

ECMO is offered when conventional regimens are ineffective. For respiratory indication, infants with meconium aspiration syndrome have the best outcomes with survival rates of 94 percent; whereas, infants with congenital diaphragmatic hernia have lower survival rates (54%). Appropriateness of the therapy in older children remains uncertain.

ECMO is being increasingly used for cardiac support, as well. The most common use is on patients

Table 46.1: International summary as of January, 2002

Group	*Total Reported*	*Number Survived to Discharge/ Transfer*	*Survival*
Neonatal respiratory	16,941	13,198	78%
Neonatal cardiac	1,605	618	39%
Neonatal ECPR	71	30	42%
Pediatric respiratory	2,216	1,210	55%
Pediatric cardiac	2,281	929	41%
Pediatric ECPR	118	43	36%
Adult respiratory	721	370	51%
Adult cardiac	343	111	32%
Adult ECPR	69	22	32%
Total	**24,365**	**16,531**	**68%**

ECMO registry report of the Extracorporeal Life Support Organization (ESLO) 2002.

Table 46.2: Neonatal respiratory case statistics-international summary as of January, 2002

Primary diagnosis	Total	Number survived	Survival
CDH	3,816	2,063	54%
MAS	5,976	5,612	94%
PPHN/PFC	2,471	1,943	79%
RDS/HMD	1,333	1,120	84%
Pneumonia/sepsis	2,475	1,828	66%
Air leak syndrome	87	60	69%
Other	985	652	66%

ECMO registry report of the Extracorporeal Life Support Organization (ESLO) 2002.

Table 46.3: Pediatric respiratory case statistics-international summary as of January, 2002

Primary diagnosis	Total	Number survived	Survival
Bacterial pneumonia	228	118	52%
Viral pneumonia	622	381	61%
Aspiration	160	103	64%
Pneumocystis	17	7	41%
ARDS	288	155	54%
Other	937	461	49%

ECMO registry report of the Extracorporeal Life Support Organization (ESLO) 2002.

Table 46.4: Cardiac case statistics-international summary as of January, 2002

Primary diagnosis	Total	Number survived	Survival
Congenital defect	3,093	1,168	38%
Cardiac arrest	115	30	26%
Cardiogenic shock	115	49	43%
Myocarditis	122	73	60%
Cardiomyopathy	274	130	47%
Other	642	248	39%

ECMO registry report of the Extracorporeal Life Support Organization (ESLO) 2002.

with intractable cardiac failure after cardiothoracic surgery,[1,2] but patient outcomes depend mainly on the etiology of the cardiac failure. Overall, there has been an increase in the number of these indications resulting in better outcomes, which is probably due to increased experience.[3]

Most recently, ECMO has been used as a tool for resuscitation on patients with cardiopulmonary arrest,[4-6] and some centers have used ECMO for support of donor abdominal organs.[7]

The prediction of mortality in pediatric patients is more difficult due to the coexistence of multiorgan failure. Matching for diagnosis and severity of illness, ECMO-treated patients had a 74 percent survival vs 51 percent survival in non-ECMO-treated patients.[8] This study shows that when used appropriately, survival in some patients is enhanced by ECMO.

Patient Selection Criteria

Determining that a patient is unresponsive to "maximal medical therapy" and considering the use of ECMO remains difficult and controversial. Most criteria have evolved from the neonatal ECMO experience.[9,10]

Defining criteria that will predict mortality in infants using conventional therapy continues to be elusive. Common criteria for the selection of ECMO candidates are shown in Table 46.5. The general eligibility criteria for pediatric ECMO are shown in Table 46.6.

Technique

The two basic types of ECMO are venoarterial (VA) and venovenous (VV). This terminology describes the direction of blood flow. The outflow is always venous, but the inflow can be arterial (VA) or venous (VV).

Table 46.5: Criteria for ECMO

1. Alveolar-arterial oxygenation difference ($AaDO_2$):
   (Predicted Mortality greater than 80%)
   $> 610 \times 8$ hr or $> 605 \times 4$ hr if PIP > 38 cm H_2O
2. Oxygenation index (OI)
   OI > 40 predicted mortality > 80%
   OI > 25-40 predicted mortality 50-80%
3. Acute deterioration:
   $PaO_2 < 40$ mmHg × 2 hr and/or pH < 7.15 × 2 hr
4. Unresponsiveness
   $PaO_2 < 55$ mmHg and pH < 7.40 × 3 hr
5. Barotrauma (any 4 of 7 simultaneously)
   - Pneumothorax
   - Pneumopericardium
   - Pneumoperitoneum
   - Pulmonary interstitial emphysema
   - Persistent air leak > 24 hr
   - Mean airway pressure > 15 cm H_2O
   - Subcutaneous emphysema

Data adapted from Georgetown University Hospital Pediatric ECMO program, Washington, DC, 1997.

Table 46.6: General eligibility criteria for ECMO

Ventilator support of < 7days duration
General ventilator setting:
- PIP > 35
- PEEP > 10
- Mean airway pressure > 18 cm H_2O
  OI > 40
  PaO_2 FiO_2 < 150
  Failure of other therapies
  - Pressure limited, inverse-ratio ventilation
  - Surfactant
  - High-frequency ventilation
  - Permissive hypercapnia
  - Inhaled nitric oxide

Data adapted from Georgetown University Hospital Pediatric ECMO program, Washington, DC, 1997.

Outflow of blood in VA and VV ECMO is from the right atrium through a catheter placed through the right internal jugular vein. In older patients, other venous sites have been used. In VA mode, after oxygenation in the ECMO circuit, the blood is returned to the patient through an arterial cannula, which is placed in the ascending aorta through the right common carotid artery (Fig. 46.1). A cannula can also be placed directly into the right atrium and the aorta through a sternotomy.

Patients with profound left ventricular failure need a left atrial or ventricular catheter to obtain decompression of the left heart. The artery that was cannulated is permanently ligated. The effect of this is unknown.[11,12] Some centers have begun repairing

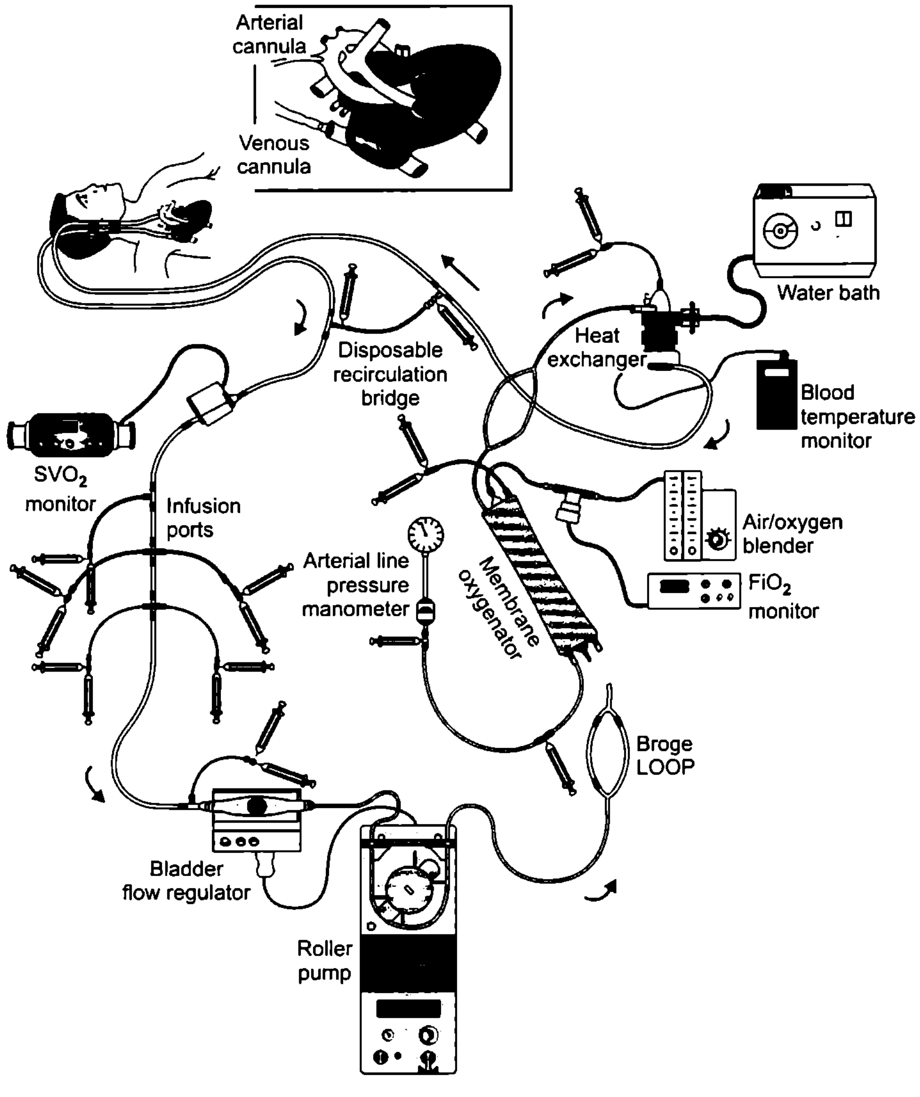
Arterial cannula
Venous cannula
Water bath
Heat exchanger
Disposable recirculation bridge
Blood temperature monitor
SVO_2 monitor
Infusion ports
Arterial line pressure manometer
Membrane oxygenator
Air/oxygen blender
FiO_2 monitor
Broge LOOP
Bladder flow regulator
Roller pump

Fig. 46.1: ECMO circuit

the artery at decannulation.[13] Repairs had an early patency rate of 90 percent in some centers.[14]

Patients with normal cardiac function, as well as those with severe pulmonary disease, may be candidates for VV ECMO support. A double lumen venous cannula has been used in neonates, and in adults, the blood is returned to the distal iliac vein of the inferior vena cava. The blood first enters a small bladder that is attached to a servo-regulated box connected to a roller pump. Inadequate blood return triggers an alarm on the bladder box, which in turn, shuts the pump off. When the bladder refills, the pump restarts. This process prevents excessive negative pressure, which otherwise might result from a kinked cannula or hypovolemia, and more importantly, prohibits the formation of air bubbles.

After exiting the bladder, the blood is actively pumped by a roller pump into a membrane oxygenator. The oxygenator consists of a hollow silicon envelope placed inside a silicone sleeve. The blood flows on the outside of the coiled envelope, and the gas flows in a counter-current direction inside the membrane. The size of the membrane is chosen according to patient size. There is an effective gas exchange here. Next, the blood flows into a heat exchanger, and then, it is infused back into the patient. The ECMO circuit is designed with a bridge that allows the child and the circuit to be isolated from one another. The blood is heparinized, and the heparin effect is measured by activated clotting time (ACT), which is maintained at 180-220 seconds. ACT can be measured at the bedside.

ECMO Management

Cannulation is done at the bedside under deep sedation and neuromuscular blockade. An initial bolus of heparin (100-200 units) is given just prior to the cannulation, after which a heparin infusion is started and continued throughout the duration of the ECMO. The flow is initially started low by 50 ml/kg/min and gradually increased by 50 ml increments. Infants need 100-200 ml/kg/min for adequate perfusion and oxygenation, although there are patients who may need more. Pediatric patients usually need 90 ml/kg/min to achieve the same goals. In VA ECMO, as the flow is increased, the left ventricular output decreases, and the arterial waveform becomes less pulsatile.

Stored blood is used to prime the circuit, which may be acidotic and calcium depleted. Using THAM (tromethamine) or bicarbonate in the priming fluid can correct acidosis. It is also recommended to measure the electrolyte concentration of the stored blood. Patients will need intermittent blood products transfused. Fresh frozen plasma may be needed intermittently to replenish clotting factors. The ECMO circuit also sequesters platelets, and counts of 80,000-100,000 are maintained routinely.

Adequacy of nutrition is maintained by initiation of hyperalimentation, and early enteral feeds are not a contraindication. Diuretics may be needed to prevent fluid retention.

While on a ventilator, patients are placed on relatively non-traumatic settings to promote lung healing. A PIP of 18-25 mm H_2O, with a PEEP of 4-5 mm H_2O, is generally used at the Children's Hospital of Wisconsin. The ventilator rates are set at 6-12 breaths per minute and the FiO_2 is 25-30 percent. Sometimes older children are managed with a PEEP of 10-12 to prevent loss of functional residual capacity.[15,16] Patients with barotrauma and air leak may benefit from high-frequency ventilation, in addition to ECMO. Typically, neonates benefit from low mean airway pressure and lung rest, and pediatric patients benefit from maintenance of functional residual capacity with higher PEEP.

When the underlying process improves, the patient is weaned to low ECMO flows (50-100 ml/kg/min) and optimal ventilator settings. A decision to decannulate is made after the patient maintains adequate oxygenation and perfusion in these settings for 2-4 hours. This weaning of flow can be achieved in slow reductions of flow rate by increments of 10-20 ml/kg/min every 1-2 hours, upto a flow rate of 50-100 ml/kg/min. During the process of weaning, blood gases and the mixed venous saturations should be frequently monitored. A more rapid weaning rate can be achieved by decreasing the flow in larger increments over shorter time intervals. Once a flow rate of 50-100 ml/kg/min has been achieved, the patient is monitored for a few hours. If deterioration is seen, high flow is re-established for 24 hours before a repeat trial is performed.

Complications

Mechanical Complications

The most common mechanical problems are oxygenator failure, tubing rupture or leak, cannula kinking, power failure, air in the circuit, and accidental decannulation.

Patient Complications

Bleeding from heparinization is a common complication. Intracranial hemorrhage is catastrophic. At the Children's Hospital of Wisconsin, daily head ultrasounds are performed on infants with open fontanels. As any other site can be involved just as easily, a high index of suspicion is needed.

Since infection is also problematic, daily surveillance cultures are ordered on all ECMO patients at the Children's Hospital of Wisconsin. Prophylactic antibiotics are not used to treat infection.

Embolization is another risk, especially with VA ECMO, and can consist of a clot, air, or particulate matter. At the Children's Hospital of Wisconsin, a bubble trap is added to the arterial side of the circuit in an attempt to reduce this risk. Sensorineural hearing loss is a long-term complication with a reported incidence rate as high as 24 percent.[17] Additionally, there is the possibility of catastrophic technical mishaps like catheter rupture, kinking of cannulae, power disruption, and accidental decannulation.

CONCLUSIONS

Presently, ECMO is viewed as an invasive procedure with significant risks, and should be used only after careful evaluation of risks/benefits and discussion with the family. However, it continues to represent an important support option in select critically ill infants and children. In the future, with increased experience, this procedure will become an even safer, more effective alternative to many less efficacious conventional therapies.

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CHAPTER

Pediatric Heart and Lung Transplantation

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Thoracic organ transplantation in children includes heart, heart-lung, and lung transplantation. This chapter will review the indications, contraindications, surgical techniques, short-term and long-term outcomes from thoracic organ transplantation.

HEART TRANSPLANTATION

Indications for Transplant

The two major indications for heart transplantation are congenital heart disease and cardiomyopathy.

The distribution of the indications differs in different age groups. In the infant age group (less than one year of age), congenital heart disease accounts for almost 3/4th, in the 1 to 10 year age group, almost 40 per cent, and in the 11 to 17 year age group, is less than 10 per cent.[1] Valvular disease, coronary disease (often congenital coronary anomalies), and retransplantation are other reported indications.[1] In infants, younger than 1 year of age, congenital heart disease, especially hypoplastic left heart syndrome, is the major indication for heart transplantation. In the 1 to 10 year age group, more than 50 per cent of patients have cardiomyopathy and approximately 37 per cent have congenital heart disease; in adolescents, 11 to 17 years of age, the main indication is cardiomyopathy in 64 per cent and congenital heart disease in 26 per cent. Pediatric cardiac transplantation has been stable in volume since the early 1990s (Table 47.1).

Table 47.1: Number of heart, heart-lung and lung transplants for the past 15 years

Year of transplant	*Heart*	*Heart-lung*	*Lung*
1988	117	11	1
1989	147	7	3
1990	213	3	9
1991	251	10	33
1992	227	10	37
1993	263	7	36
1994	252	15	31
1995	261	12	68
1996	255	10	48
1997	271	5	61
1998	258	9	62
1999	245	11	46
2000	267	8	50
2001	270	6	39
2002	254	6	44

Source: OPTN/SRTR Data as of March 31, 2003.

Waiting List

As of March 31, 2003, there were 3520 patients, less than 18 years, waiting for a heart transplant. Of these 37% were less than 1 year, 21 per cent were between 1 and 5 years, 13 per cent were between 6 and 10 years and 29 per cent were between 11 and 17 years. It is very evident that the number of donors available were quite insufficient for the number of candidates awaiting a transplant.[2] In 2009, the waiting situation is no different perhaps somewhat worse compared to 2003. In the US, once a child is determined to be an appropriate candidate for heart transplant, he or she is placed on the United Network for Organ Sharing (UNOS) waiting list. UNOS has established the following classifications for children awaiting heart transplantation:

Status 1A

The patient must meet at least one of the following criteria and have an attending physician recertify the patient every 14 days.

- The child requires a ventilator, mechanical assist device, or balloon pump
- Is less than 6 months old
- Congenital or acquired heart disease exhibiting reactive pulmonary hypertension at greater than 50 per cent of systemic levels
- Requires infusion of a high-dose single intravenous, inotrope or multiple intravenous inotropes
- Is not expected to live longer than 14 days without a heart transplant, but does not meet any of the above criteria.

Status 1B

The patient must meet at least one of the following criteria:

- Requires the infusion of a low-dose single intravenous inotrope.
- Is less than 6 months old.
- Is experiencing growth failure defined as less than the fifth percentile for weight and/or height, or loss of 1.5 standard deviations of expected growth based on the National Center for Health Statistics for pediatric growth curves.
- In utero candidate for whom prenatal diagnostic tests have confirmed that the patient is viable and medically suitable to receive a heart transplant.
- A patient who does not meet any of the above criteria but is determined to have an urgency or potential benefit comparable to that of other patients, would need to have a justification letter sent to the UNOS regional review board.

Status 2

The patient has been determined to be an acceptable candidate for heart transplantation and does not meet any of the criteria of Status 1A or Status 1B.

Status 7

The patient is currently inactive on the transplant waiting list, i.e. improvement in condition/functional status, active infection, family declines consent.

The number of pediatric registrants, listed every year for heart transplantation, has remained relatively stable since the mid-1990s. Little change was seen in the age distribution of new heart waiting list registrations, with the preponderance of pediatric heart transplant registrants aged less than one year.[2] The median time to heart transplant was substantially lower among pediatric than adult registrants. Fig. 47.1 shows the distribution of waiting times for heart transplants.

The incidence of death while awaiting heart transplantation is extremely high in registrants under 1 year (1,373 waiting list deaths per 1,000 patient years at risk). These infants often have complex congenital heart disease, are relatively unstable, and are unable to be supported adequately for longer waiting times.[2] The rate of mortality among this youngest

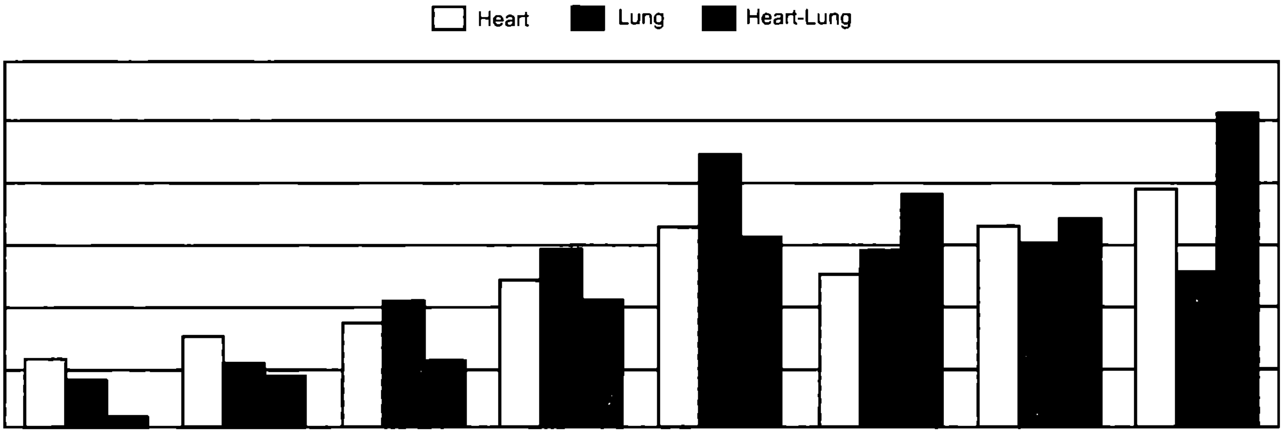

Fig. 47.1: The timing of rejection episodes after transplantation. From: Kertesz: Am J Cardiol 2001;87(5):667-68.

group was almost 10 times the overall waiting list mortality for cardiac transplantation across all age ranges. In children aged 1 to 5 years, waiting list mortality was 377 per 1,000 patient years at risk, more than twice the overall mortality for all registrants, and in those aged 6 to 10 years the rate of death, while waiting, was similar to the overall waiting list mortality.[2]

Contraindications

In children, as in adults, serious pulmonary, central nervous system, renal and hepatic dysfunction are contraindications to heart transplantation. Pulmonary hypertension may be a contraindication to transplant in some patients with dilated cardiomyopathy. High pulmonary vascular resistance (> 5 Wood units) or a transpulmonary pressure of greater than 15 mm is a potential contraindication. However, if pulmonary resistance is reactive and decreases with the administration of oxygen, nitric oxide, or prostaglandin, transplantation is not necessarily contraindicated. All patients with elevated pulmonary resistance must undergo hemodynamic testing to establish both resting and best pulmonary arteriolar resistance and transpulmonary gradient prior to transplantation or exclusion from listing. When the response is marginal, repeat values after a 1 to 2 week course of intravenous inotropic support, afterload reduction, and pulmonary vasodilatation may demonstrate improvement. Patients known to have marginal values should be tested at least every 6 months while waiting for transplantation, since reactive pulmonary hypertension may worsen and become fixed. Patients with fixed elevation of pulmonary resistance on the basis of cardiac failure may be candidates for heart-lung transplantation.

Surgical Techniques

There are three current techniques of heart transplantation. The standard technique originally described by Lower and Shumway, involves removal of both donor and recipient hearts at the midatrial level, the socalled "biatrial" technique. This preserves the pulmonary venous connections to the recipient's left atrium. There is a higher incidence of atrial dysrhythmias, atrial dysfunction, and thrombus formation.

In 1991, a new technique was introduced in which the vena cavae are resected and anastomosed—the "bicaval" technique. This procedure preserves the integrity of the right atrium.

The theoretical advantage of this technique is the preservation of atrial contractility, sinus node function, and tricuspid valve competence but takes longer to complete and prolongs ischemic time. Use of this technique also eliminates the double P wave formerly seen on posttransplant ECG bicaval.

Heterotopic heart transplantation refers to implantation of the heart not in the cardiac fossa but as a "piggyback" to the native heart. This approach prevents the patient from having to undergo a heart-lung transplant. The heterotopic procedure leaves the native heart to provide the pulmonary circulation and the donor heart to provide the systemic circulation.

The surgical techniques in pediatric heart transplantation required to treat CHD also present major challenges. In addition to replacing the heart itself, the surgeon may need to repair or reconstruct major vessels or chambers, may need to take down previously placed shunts and baffles, and dealing with issues of previous chest surgeries. These additional technical problems add to the period of ischemia for the donor heart and to bypass and cross-clamp time, which affect postoperative management and outcome. The complexity of surgery in the presence of CHD increases the risk of mortality. This is borne out in a lower overall survival rate in those with CHD than in all other indications for transplantation.[1, 2]

Some patients may need some form of mechanical cardiovascular support prior to transplantation. In adults, mechanical support is easily achieved using ventricular assist devices. In children, because of the small size and other technichal difficulties, extracorporeal membrane oxygenation is the only viable option for support as a bridge to transplant. The true left ventricular assist device (LVAD) with pneumatic or electrical drive system is rarely applied in children because of the requirement for a large body-surface area.

LUNG AND HEART-LUNG TRANSPLANTATION

Indications

Lung disease, where the patient's lungs cannot be expected to maintain adequate gas exchange and there is a high probability of death, is the general indication for lung transplantation.

Many types of lung disease may lead to end-stage pulmonary failure. In some cases, the lung disease may also severely affect the function of the heart. The failure of the lungs and/or heart results in poor quality of life and severely limited life expectancy. If the patient's condition is either not improved significantly or worsens despite maximal medical and/or surgical treatments, then they are considered to be candidates for lung transplantation.

The primary indications for lung transplants in young children include congenital malformations of the lung, pulmonary hypertension, surfactant deficiencies, and other severe forms of pulmonary fibrosis. Cystic fibrosis is a very infrequent indication for transplant in this age group. The severity of the lung diseases, therefore, may increase the risk of death while waiting for organs from an increasingly rare donor pool.

Selection of Candidates and Waiting List

Pediatric lung transplantation continues to be an infrequent procedure. New pediatric waiting list registrations for lung transplant peaked in 1998 at 152 and decreased to 109 and 115 in 2000 and 2001, respectively.[2] The causes for decreased registrations for lung transplants in the pediatric population is unclear. However, improved management of cystic fibrosis, which allows patients to achieve older ages before listing for transplant, may account for some of the decrease.[2] In addition, the contribution of living donor lobar transplantation in the pediatric population with cystic fibrosis must be also considered. Figure 47.1 shows the distribution of waiting times for lung transplant. The overall death rates while on the waiting list for the entire lung transplant group was 134 per 1,000 patient years at risk in 2001, and represents a continual decline over the decade.[2] The very youngest age groups appear to have an increased risk of death while waiting, consistent with the limited number of donors suitable for this population (due to size considerations) and the severity of the illnesses for which lung transplantation is considered.[2]

Surgical Considerations

There are four options for lung transplantation:

- Replacement of a lobe (lobar transplantation)
- Replacement of one lung (single lung transplantation)
- Replacement of both lungs (double lung transplantation)
- Replacement of both lungs and the heart (heart-lung transplantation).

The type of transplant operation which is chosen depends on the specific type of lung disease, patient's heart function, the patient's size, and the source of the organ. With living-related donation, only lobar and single lung transplants are viable options. Indications for single lung transplantation may include pulmonary fibrosis, pulmonary hypertension, and congenital malformations of the lung and only if somatic growth is nearly complete and the lung offered is perfect size and health. Indications for double lung transplantation include pulmonary fibrosis, primary pulmonary hypertension and other types of pulmonary vascular disease, severe interstitial lung disease, cystic fibrosis, pulmonary hypertension with structural heart defect(s) amenable to surgical repair, surfactant B protein deficiency, alveolar proteinosis, and bronchiolitis obliterans. The decision to undergo a heart-lung transplantation will be based on the above indications and a failing heart. For heart-lung transplants, the organs are removed en bloc. The current practice is to use bibronchial anastomosis for transplanting the lungs and a bicaval anastomosis for transplanting the heart.

PHYSIOLOGY OF THE TRANSPLANTED HEART

Hemodynamics

Cardiac function immediately after transplantation depends on several factors which include ischemic/preservation time, effects of cardiopulmonary bypass, and the pulmonary vascular resistance. Immediately after transplantation the cardiac output and diastolic compliance are diminished, attributable to the anoxic period experienced from the time of harvest to transplantation.[3]

The mechanisms involved in the decreased diastolic compliance include myocardial swelling, altered intracellular calcium metabolism leading to impaired myocardial relaxation and interstitial edema. These effects peak in 24-48 hours and then improve. Contractility, ventricular compliance, and cardiac performance improve over the next several days. The transplanted heart is a denervated heart; therefore, the resting heart rate is faster than normal due to the loss of parasympathetic inhibition and is only responsive to circulating catecholamines and not to intrinsic neural reflexes. In the early postoperative phase, both right and left ventricular filling pressures are increased but they decrease slowly with time. The surgically denervated heart responds differently to physiologic demands. Without autonomic innervation, the heart's response to hypovolemia and hypotension is impaired. Although the posttransplant patient lacks neural response mechanisms, the heart does respond to increased venous return with an increase in stroke volume in accordance with the Frank-Starling curve. The heart also responds to circulating catecholamines with an increase in rate and output. Late hemodynamics seem to be related to the immunosuppressive regimen employed. Patients maintained on azathioprine and prednisone often have normal cardiac output, normal to elevated pulmonary wedge pressure, normal pulmonary artery pressure, normal EF, and normal blood pressure. With cyclosporine, the incidence of systemic hypertension is increased which may lead to high left ventricular filling pressures, high pulmonary capillary wedge pressures and high right atrial pressures. Myocardial contractility remains comparable to normal native hearts.[4]

The transplanted heart can respond to exercise by increasing its rate from circulating catecholamines released from the peripheral nervous system, but the rate of increase is delayed.

Early in the exercise, there is an increase in cardiac output due mainly to an increase in end-diastolic volume and stroke volume unlike the normal heart which increases cardiac output initially by an increase in heart rate. At maximal exercise, there is an increase in the heart rate, ejection fraction, and stroke volume all due to the increase of circulating catecholamines.

PHYSIOLOGY OF THE TRANSPLANTED LUNG

Just as with the heart, the transplanted lung or lung segment is denervated. Therefore, there is no afferent input for the brain from the lung. The lung seems to be more susceptible to reperfusion injury than the myocardium. This injury is manifest by both interstitial and alveolar injury and presents as acute lung injury which may progress to ARDS. Initially, after transplant, there may be mucosal swelling leading to lower airway obstruction. These effects peak at 24-48 hours and recover over the next several days.

Perioperative Care of Infants and Children after Thoracic Organ Transplant

Infants and children undergoing thoracic organ transplantation require critical care both before and after transplantation. A multi-disciplinary approach involving the pediatric cardiac surgeons, pediatric intensivists, and pediatric cardiologists is optimal in the management of these patients. This section

Table 47.2: Goals of perioperative management of infants and children after thoracic organ transplantation

Preoperative goals
- Stabilization of cardiovascular status
- Support of respiratory and circulatory systems
- Accurate assessment of the cardiovascular status and need for transplant

Preoperative preparation
- Correction of metabolic and acid-base imbalances
- Support of respiratory and circulatory systems
- Maintenance of secondary organ function
- Adequate nutrition
- Prevention of secondary insults to the myocardium
- Prevention of secondary injury to other organs

Postoperative goals
- Minimize the workload on the heart and lungs
  - Airway control
  - Mechanical ventilation
  - Temperature control
  - Optimize preload and afterload
- Maintain adequate tissue perfusion
  - Optimize preload and afterload
  - Support and maintain contractility
- Maintain metabolic and acid-base balance
- Prevention of secondary insults to the myocardium
- Prevention of secondary injury to other organs
- Withdrawal of external cardiopulmonary support

provides a brief overview of the goals of management and guiding principles for the perioperative care of the infant and child after thoracic organ transplantation.

The goals of perioperative management are given in Table 47.2.

Initial Assessment

Postoperative assessment in the ICU must be performed soon after arrival. The components of the initial postoperative assessment includes the following:

1. Review the preoperative anatomy, physiology and interventions.
2. Review the intraoperative events and the current postoperative anatomy.
3. A thorough evaluation of the cardiac and respiratory systems.
4. Laboratory analyses (chest X-ray, electocardiograph, blood gas analysis, complete blood count, serum electroytes including ionized calcium, serum glucose, and coagulation profile, if necessary).
5. Current cardioactive agent use.

Critical Care Issues after Thoracic Organ Transplantation

Cardiovascular Issues

Cardiac output is determined by heart rate, preload, contractility, and afterload. An adequately filled-heart is important. The determinants of diastolic filling of the heart are heart rate which affects diastolic filling time, venous return, distensibility of the ventricles, pericardial restraint, and the presence or absence of synchronized atrioventricular contraction. Inadequate venous return is manifested by low filling pressures. Decreased ventricular distensibility is manifested by the presence of high filling pressures coupled with a small heart on a chest X-ray or by echocardiograph. Decreased ventricular distensibility may be due to a stiff myocardium, poor ventricular relaxation, or enrachment by the opposite ventricle through the interventricular septum. Decreased ventricular filling may result from pericardial fluid collection, most commonly due to bleeding, postoperatively. Atrioventricular dissociation results in asynchronous contraction of the atria and ventricles with the loss of the "atrial kick" which may account for a substantial amount of diastolic filling (20-25%). Systolic dysfunction is due to decreased contractility. After cardiopulmonary bypass, there is often decreased high energy phosphates, decreased oxidative phosphorylation, and increased glycolysis in a dysfunctional heart. Internal work takes precedence over external work. Coronary blood flow is affected by diastolic pressure, diastolic time, increased filling pressure, increased wall tension, and myocardial edema which increases the perfusion pressure required for coronary blood flow.

Improvement of Cardiac Function

An adequate preload is a prerequisite for optimal heart function after transplant. It is more important to assess the impact of volume loading on the changes in filling pressures than any specfic absolute pressure value. For example, if a 5 mL/kg of fluid bolus results in a change in central venous pressure from 10 to 20 mmHg, that would suggest that the ventricle is stiff and the pressure-volume curve is at the high end of the compliance curve. Further volume loading of this patient is unlikely to result in an improvement in cardiac output but may result in edema and pleural effusions. On the other hand, if the change in central venous pressure is minimal (from 8 to 10 mm Hg), then the ventricle is more compliant and there is a good likelihood of improvement in cardiac output. Postoperative hemodynamic instability is usually multifactorial and mechanisms involved include myocardial injury related to prolonged ischemic time, cardiopulmonary bypass, preoperative hemodynamic instability and myocardial dysfunction, and reperfusion injury. Intraoperative echocardiography and full hemodynamic monitoring are utilized to detect changes in hemodynamic parameters. Inotropic support with beta-adrenergic catecholamines is used routinely for the first few days. In the past, the drug of choice was isoproterenol. More recently, dobutamine is the mainstay of intravenous inotropic support. Other drugs that may be used include epinephrine, norepinephrine, milrinone, prostaglandin E1, and nitroprusside. Dysrhythmias may lead to hemodynamic instability in the early postoperative period. A resting tachycardia is common without vagal innervation. Mild-to-moderate pulmonary hypertension may be seen, especially in the very young and often require inhaled nitric oxide to relax the vascular smooth muscle and decrease PVR. Pulmonary artery pressures typically return to normal during the first month after transplantation. All adrenergic inotropes increase myocardial oxygen demand. Hypocalcemia is common after cardiopulmonary bypass or in infants with DiGeorge syndrome and impairs contractility. Maintaining an ionized calcium level >1.0 mg/dl improves cardiac contractility. Afterload reduction is an important component of cardiac support. Nitrosovasodilators and milrinone are the most common agents used to decrease ventricular afterload.

Pulmonary Dysfunction

After Heart Transplant

Pulmonary dysfunction after heart transplant is due primarily to myocardial dysfunction. When there is moderate to severe myocardial dysfunction, it is common to see respiratory system dysfunction.

This can be manifested as a decrease in respiratory reserve, an increase in respiratory work, and an effect on gas exchange. Respiratory failure results when the cardiovascular system fails to meet the increased metabolic demands imposed by the respiratory muscles. Positive pressure ventilation, by unloading the respiratory muscle work, can decrease the metabolic demand and work load of the heart. Therefore, moderate to severe cardiovascular dysfunction is a major indication for continuation of mechanical ventilation after heart transplantation. Respiratory failure may also result from parenchymal injury to the lung during cardiopulmonary bypass or due to reperfusion injury. Positive end-expiratory pressure is often necessary to recruit the lung. The ventilator settings need to be titrated to optimize the beneficial effects while minimizing the negative effects of positive pressure breathing.

After Lung Transplantation

Pulmonary dysfunction after lung transplantation is due to several factors including reperfusion injury, altered lymphatic drainage leading to lymph accumulation in the lung, and hyperacute rejection. Reperfusion injury manifests itself as worsening gas exchange in the hours to days after transplant with a reduction in lung compliance and the presence of perihilar infiltrates.[5] This diagnosis should be considered after the exclusion of volume overload, rejection, pneumonia, or vascular compromise. Cardiopulmonary bypass seems to be the principal factor that is associated with an increased incidence and severity of the reimplantation response. Other causes of acute lung dysfunction in the immediate posttransplant period are aspiration, contusion, or inadequate lung preservation. Graft failure, secondary to bronchial dehiscence, can occur early in the transplant experience.

Perioperative Pain and Sedation

Adequate pain control has been shown to decrease the stress response after transplant. Pain increases ventricular afterload and imposes a burden on myocardial oxygen demand. Adequate sedation is sometimes necessary to decrease patient-ventricular asynchrony, which is common in neonates and infants after transplant. Older children and adolescents may benefit from patient-controlled analgesia.

Metabolic Demands and Nutritional Support

Metabolic demands are increased after transplantation. Fever is a strain on the heart by increasing its metabolism. Adequate nutrition is key in the postoperative management. As soon as it is feasible, enteral feedings must be encouraged. Electrolyte imbalances are common after cardiac surgery with the use of diuretics. It is important to maintain normal metabolic balance. In infants and children, it is critical to maintain normal glucose, potassium, acid-base, calcium, and magnesium balance.

Immunosuppression

Immunosuppressive regimens used in pediatric thoracic organ transplant recipients tend to be both individual and institution-specific.

Regimens for induction of immunosuppression usually employ a combination of drugs that act at various sites. A T-cell activation inhibitor—either a calcineurin inhibitor, such as cyclosporine or tacrolimus or less commonly sirolimus (rapamycin), a new T-cell activation inhibitor, that acts independent of calcineurin inhibition is the mainstay of immunosuppression.[6] In addition, most patients also receive an antiproliferative agent, either MMF or azathioprine. Children often also receive corticosteroids.

Cyclosporine and tacrolimus are titrated based on serum levels which are measured frequently at first and then periodically. Once induction is achieved, the steroids are weaned to very low maintenance levels. An attempt is made to discontinue long-term corticosteroids completely.

Cyclosporine is the most commonly used immunosuppressant following pediatric heart transplantation. Both formulations of cyclosporine (Sandimmune and Neoral) have been used in pediatric transplantation. Usual doses of cyclosporine range from 5 to 10 mg/kg/d. Cyclosporine trough levels are usually maintained in the range of 100 to 300 ng/mL. Tacrolimus is an alternative to cyclosporine. The usual oral dose range of tacrolimus is from 0.05 to 0.1 mg/kg/d; the intravenous dose range is 0.01 to 0.05 mg/kg/d. Tacrolimus trough levels are usually maintained in the range of 5 to 15 ng/mL. Armitage *et al* reported on 26 children who received transplant under tacrolimus-based immunosuppressive therapy. Early, nonrandomized clinical experience suggested that tacrolimus-treated children had similar left ventricular function, experienced fewer episodes of severe rejection, were more rapidly weaned from corticosteroids, and had relatively few side effects from immunosuppression compared with cyclosporine-treated children.[7] Survival, in this group was 82 per cent at 1 and 3 years. Notably, the actuarial freedom from grade 3A rejection in the tacrolimus group, was 60 per cent at 3 and 6 months versus 20 per cent and 12 per cent, respectively, in 15 children treated with cyclosporine-based triple-drug therapy ($P < 0.001$). Children treated with tacrolimus do not experience hirsutism, gingival hyperplasia, or abnormal facial bone growth associated with cyclosporine-based immunosuppression.[8] A potential benefit of tacrolimus over cyclosporine is less elevation of total and low-density lipoprotein cholesterol.[9] Recent comparisons with randomized trials have not seen this clear benefit of tacrolimus in reducing rejection frequency.[10] Serious concerns have limited the enthusiasm for tacrolimus as the first-line calcineurin inhibitor in many pediatric heart transplant centers. The first is the development of insulin-deficient diabetes that was reported in 2 of 50 (4%) heart recipients.[11] The second is the potentiation of Epstein-Barr virus (EBV)-mediated lymphoproliferative disease after transplant,35 because many pediatric recipients are EBV negative at time of transplant.[12] Third, tacrolimus may have higher risk of coronary vasculopathy after transplant compared with cyclosporine.[13] Corticosteroids are used for induction in all pediatric patients at the moment. For induction, prednisone/methylprednisone is administered at a dose of 1 mg/kg/d tapered to 0.1-0.2 mg//kg/d. About 75 per cent of pediatric recipients initially receive maintenance corticosteroids; however, after several years, at least half of pediatric heart recipients have been withdrawn from corticosteroids.[14-16] Long-term corticosteroid usage in pediatric heart transplantation has been linked to higher risks of opportunistic infections, diabetes, bone demineralization, and graft coronary artery disease have been linked to immunosuppressive regimens containing steroids or to their "steroid burden". Notably, it has been reported from a number of centers that successful heart transplantation can be performed in pediatric recipients without the use of maintenance steroids in the immunosuppressive regimen.[17,18]

In light of current data, many programs try to minimize the dose and duration of corticosteroid therapy after pediatric heart transplantation. Azathioprine and MMF are the two most common adjuncts to the calcineurin inhibitors for maintenance immunosuppression in pediatric transplantation. Azathioprine is usually administered in the range of 1 to 3 mg/kg/d. Azathioprine dosing is generally based on the serial white blood cell count. Mycophenolate mofetil has recently been substituted for azathioprine. MMF is converted to mycophenolic acid, which acts as an inhibitor of purine synthesis via the *de novo* pathway. Lymphocytes lack a salvage pathway, thus, MMF is an effective and relatively specific immuno-suppressive antilymphocyte agent. Because MMF reduces available guanine nucleotides, cell cycling is inhibited and clonal expansion, a required step in an immune response, is reduced. Studies comparing MMF with azathioprine have shown MMF to be more efficacious in adult heart transplant recipients.[19] Absorption and metabolism of MMF varies with age, other drugs in the regimen, and time after transplant. Hence, the starting dose for MMF varies widely, ranging from 30 to 150 mg/kg/d. Maintaining trough serum mycophenolic acid levels between 2 and 4 relate to efficacy and should be monitored in the patient receiving MMF. Sirolimus (rapamycin) is a newly introduced antiproliferative with a novel mechanism of immunosuppression. Sirolimus blocks the co-stimulatory signal mediated by NF-B and can act synergistically with the calcineurin inhibitors that block IL-2 signalling.[20] Indications for use of sirolimus following pediatric heart transplantation remain to be defined. However, by extrapolation with indications in other solid organ transplantation, sirolimus could be useful to withdraw or reduce dose of the calcineurin inhibitors for toxicity or EBV-mediated lymphoproliferative disease after transplant.[7]

Post-transplant Problems

The posttransplant problems are listed in Table 47.3. Some are common to all thoracic surgeries and some are specific to the transplants performed. Thoracic organ transplant recipients are at a higher risk for perioperative bleeding due to preoperative anticoagulation, passive liver congestion, and previous chest surgery.[21-24] The intraoperative use of the proteinase inhibitor, aprotinin, has been reported to inhibit fibrinolysis and significantly diminish bleeding associated with major cardiovascular procedures.[21-24] Postoperative respiratory therapy is necessary to prevent pulmonary complications. Physical reconditioning is started as soon as the patient is stable hemodynamically. Most recipients are able to exercise normally and generally report good functional capacity and life satisfaction.[25,26]

Table 47.3: Post-transplant problems

Immediate perioperative problems

Related to any thoracic or cardiac surgery
- Bleeding
- Pain
- Liberation from mechanical ventilation

Related to specific transplantation
- Acute graft dysfunction

Late Postoperative problems
- Acute rejection
- Infections

Chronic problems
- Chronic rejection
- Infections
- Malignancies
- Graft failure

Diagnosis and Management of Rejection

Types of Rejection

There are three types of rejection—hyperacute, acute, and chronic rejection.

Hyperacute rejection occurs when the host has been previously sensitized (preformed anti-bodies) to the donor's I-MHC antigens. This is a humorally mediated response and a vascular phenomenon typically occurring during or shortly after implantation. Thrombosis and whole organ ischemic necrosis occurs with or without antibody deposition in the parenchyma and has a very dismal prognosis.

Acute rejection occurs within the first three months after transplantation. It is a cell-mediated response and is the consequence of the activation of the native T-cells and their proliferation.

Chronic rejection occurs probably in response to vascular antigens other than HLA antigens. This leads to fibrointimal proliferation resulting in diffuse vascular occlusion, ischemia, and infarction and the mechanism involved are poorly understood. Approximately one-third of patients are rejection-free. Rejection that occurs more than 2 years after transplantation has been linked to poor compliance with the immunosuppressive regimen.

Rejection after Cardiac Transplants

Rejection is defined by the Pediatric Heart Transplant Study Group as the clinical decision to intensify immunosuppression in association with either histo-pathology or dysfunction.[27] Acute cellular rejection is fatal in less than 10 per cent of episodes.[28] Using current immunosuppressive regimens, pediatric heart transplant recipients experience an average of 1.5 to 2 rejection episodes in the first 3 years after transplantation.[29]

Diagnosis

Early diagnosis and immediate administration of the appropriate immunosuppressive regimen to halt the process are the keys to managing rejection. Histopathology in cardiac tissue obtained by endomyocardial biopsy has been considered the gold standard for diagnosis of acute cardiac allograft rejection. Endomyocardial biopsies are performed using a biotome inserted percutaneously through the right internal jugular vein. Small samples of the right ventricular wall are examined microscopically for evidence of and severity of rejection. The allograft is sampled about a week to 10 days after implantation and then periodically with a higher frequency at first and less later. The likelihood of acute rejection diminishes with time. Limitations of endomyocardial biopsy for diagnosing acute rejection are sampling error with a reduction in sensitivity, observer variability of interpretation, quality of specimens, and presence of vascular rejection.[30]

Histologic Grades of Rejection

The numbers of infiltrating lymphocytes and the presence of myocyte injury are used to grade rejection and to guide to rejection therapy.

Mild acute rejection is defined by the presence of perivascular or mild interstitial lymphocytic infiltrates without myocyte destruction. It is generally unaccompanied by any hemodynamic compro-mise.

Moderate acute rejection is characterized by marked perivascular, endocardial, and interstitial lymphocytic infiltrates with loss of myocytes.

Severe acute rejection is characterized by the presence of marked myocyte necrosis, hemorrhage, and neutrophil infiltration characteristic of acute inflammation.

A histologic classification system, developed by the International Society for Heart and Lung Transplant, is used to grade the biopsy between 0 to 4.[31] A Grade Zero shows no evidence of acute rejection. Grade 1A is associated with mild focal perivascular interstitial infiltrate and Grade 1B is associated with mild interstitial infiltrates as well. Grade 2 rejection is associated with moderate focal interstitial infiltrates. Grade 3A shows moderate multifocal lymphocytic infiltration with myocyte damage and Grade 3B shows a more diffuse inflammatory process with myocyte damage. Grade 4 shows severe diffuse lymphocytic infiltration with hemorrhage, necrosis, and vasculitis. The current practice is to intensify immunosuppression, usually first with pulse corticosteroids, if the biopsy score is 3 or greater.

Noninvasive Assessment of Acute Rejection

Currently, there is no reliable noninvasive test for acute rejection after heart transplantation.[32,33] A prolongation of isovolumetric contraction time and isovolumetric relaxation time and abbreviation of ejection time in echocardiographic hemodynamics can often suggest acute rejection but without a biopsy, it is difficult to ascertain the reason for the changed hemodynamics.[34] A reduced systolic function reportedly have high specificity but low sensitivity,[35] in part because systolic dysfunction is a late finding. Diastolic dysfunction, as determined by echocardiography, has high sensitivity but low specificity, in part because diastolic parameters are load-dependent and abnormal in a significant

Table 47.4: Noninvasive techniques for diagnosing acute cardiac rejection

Allograft imaging techniques (form and function)
- Wall motion analysis using pulsed wave-tissue Doppler imaging
- Acoustic quantification to measure cardiac volumes
- MRI and spectroscopy

Electrical event monitoring
- Ventricular evoked response amplitude assessment
- Spectral analysis of heart rate variability
- Signal-averaged electrocardiography

Peripheral markers for intragraft events
- Coagulation markers (prothrombin fragments and P-selectin)
- Complement and leukocyte membrane activation markers
- Natriuretic peptides (b-type natriuretic peptide)
- Ultrastructural cardiac enzymes (troponins and creatine kinase MB isoenzyme)
- Markers of nitric oxide generation (serum nitrates and cyclic GMP)
- Prostaglandin (thromboxane) and neurohumoral (endothelin) markers
- Inflammatory markers (C-reactive protein, cytokines, adhesion molecules)

Allograft imaging for necrosis and apoptosis
- Indium antimyosin imaging
- Annexin-V imaging for intragraft apoptosis

number of recipients in the absence of rejection.[36] Some of the noninvasive tech-niques for detecting and diagnosing acute cardiac rejection are shown in Table 47.4.[37] Cardiac troponin T increases and remains elevated for at least 1 month during acute rejection. The diagnostic power of a single cTnT measurement was not sufficient to replace endomyocardial biopsy.[38]

Acute Rejection after Lung Transplantation

Hyperacute rejection is rare after lung transplantation. Hyperacute rejection occurs within minutes to hours after transplantation. Clinically, hyperacute rejection in the pulmonary allograft has been associated with a positive T-cell cross-match and diffuse alveolar damage.[39] Another case of hyperacute rejection is described as characterized by interstitial neutrophilic infiltration, with platelet and fibrin thrombi and antibody deposition on the endothelial surface and vessel walls.[40] Hyperacute rejection, which is extremely rare, must be distinguished, clinically from ischemia-reperfusion injury, which is likely present in most lung transplant recipients. Fulminant hyperacute rejection is almost uniformly fatal.

Acute Rejection

Acute rejection typically occurs in the first 3 to 6 months after transplantation. Most recipients have at least one episode. The risk remains after this time, and later episodes of rejection are not uncommon. The acute rejection response includes both a cellular response and soluble mediators, whereas hyperacute rejection is considered primarily a humoral response. The degree of HLA mismatching, especially at HLA-DR and HLA-B loci, appears to be a risk factor for acute rejection.[41, 42] Transbronchial biopsy has been of use in the asymptomatic patients with rejection, in which routine surveillance biopsies have revealed histologic evidence of minimal to mild grade rejection. Not infrequently, radiography is unrevealing.[43] When rejection is symptomatic, patients may complain of fever, cough, dyspnea, or anorexia. Spirometry is a useful adjunct; declines in home spirometry of 10 to 15 per cent usually prompt a search for acute rejection. A decrease in FEV1, vital capacity, and diffusion capacity have a sensitivity of greater than 80 per cent to detect acute rejection or infection episodes.[44] However, specificity is low because deterioration in pulmonary function parameters does not point to an etiology of pulmonary dysfunction.[45] Bronchoscopy with biopsy aids in the diagnosis of rejection. The key histologic finding is perivascular lymphocytic infiltrates, which may be in association with lymphocytic bronchitis or bronchiolitis. Eosinophilic alveolitis has been associated with allograft rejection.[46] Despite characteristic pathology and spirometry suggestive of acute rejection, infection and rejection do not infrequently occur together.

Management of Acute Rejection

Infection should be excluded before an augmentation of immunosuppression. Treatment of acute rejection has traditionally been based on the use of high-dose corticosteroids, which exert a broad-spectrum immunosuppression. Corticosteroids can induce apoptosis of activated lymphocytes, terminating the rejection process. However, steroid resistant rejection does occur and usually requires treatment with an anti-T-cell antibody, either the polyclonal ATG or the monoclonal anti-CD3 antibody. Recalcitrant rejection has also been treated with antiproliferative agents, e.g. methotrexate or cyclophosphamide. Anecdotal success has been reported with the use of total lymphoid irradiation and plasmapheresis.

CHRONIC REJECTION AND PROBLEMS AFTER TRANSPLANTATION

Common to all Transplants

Infection

Infection, caused by multiple factors including immunosuppression, surgery, invasive devices, and predisposing factors, is a significant cause of morbidity and mortality after organ transplantation in pediatric patients.[47] Immunosuppressive agents, necessary to prevent and treat rejection diminish host defenses and predispose to infection. Infection is the leading cause for readmission to the hospital after transplantation and occurs in 21 per cent of pediatric heart transplant recipients in the first year after transplantation.[48] Bacterial infections are the most common, followed by viral, fungal, and protozoal infections. In infants less than 6 months of age, bacterial infections were most likely to occur within the first month after transplantation, and occurred most often in the blood and lungs. Viral infections usually emerged in the second month after transplantation.[1] Cytomegalovirus (CMV) infection is more common in donor-positive, recipient-negative mismatches, but death due to CMV is low. Infection with Candida, the leading infectious agent in fungal infections, carries a high mortality rate. The rate of infectious complications is higher in lung transplant patients as compared to recipients of other solid organs.[49,50] This may be due to donor airway colonization, impairment of the cough reflex and mucociliary clearance.[51,52]

Malignancy

Lifelong immunosuppression therapy brings with it the threat of neoplastic disease from diminished cancer cell surveillance. The transplant tumor registry reported 354 instances of malignant disease in children who underwent transplantation (all organs) from 1968 through 1993. Those tumors consisted of lymphomas (52%), skin and lip cancers (20%), sarcomas (6%), carcinomas of the vulva and anus (4%), and hepatic (3%) and thyroid (3%) carcinomas. The lymphomas were largely (98%) non-Hodgkin's lymphoma and were the most frequent form of malignant disease in nonrenal transplant recipients (83%).[53] Two single-center reports, from Children's Hospital of Pittsburgh and Lucille Packard Children's Hospital at Stanford, describe the incidence of posttransplantation lymphoproliferative disorder (PTLD) as 7.7 to 8.5 per cent in pediatric heart transplant recipients.[54,55] Clinical characteristics included fever, malaise, sore throat, lymphadenopathy, splenomegaly, gastrointestinal distress, anemia, neutropenia, and pulmonary nodules visible on chest radiograph. *In situ* hybridization showed the presence of Epstein-Barr virus (EBV) in all cases.[54,55] A significant association between PTLD and primary EBV virus infection was noted. None of the children in Pittsburgh with positive serology before transplantation experienced PTLD, suggesting that prior infection had a protective effect.[54] Ten of the 30 children with primary EBV infection had PTLD (33%) and another 8 of 17 in whom EBV seroconversion had occurred, had PTLD (47%). It was also noted that disseminated disease (multiorgan involvement) at initial examination was a poor prognostic indicator with no survivors.[54] The Stanford outcome showed 50 per cent survival with 40 per cent of deaths related to neoplastic disease itself and 20 per cent each to rejection, renal failure, and infection.[55] The survivors were disease-free from 1.5 to 15.5 years. Some have noted a higher incidence of PTLD in the pediatric patients who were transplanted for cystic fibrosis.[56] In these patients, the only risk for PTLD was two or more episodes of acute rejection within 3 months posttransplant. Epstein-Barr virus or cytomegalovirus serologies, age, and the use of antithymocyte and antilymphocyte globulins were not risk factors. Treatment of PTLD consists of reduction or discontinuation of immunosuppression and in some cases, antiviral therapy, including interferon therapy. Monoclonal antibodies directed against CD20 are available and have been used for the treatment of PTLD in lung transplantation patients.[57]

Side Effects of Drugs

Significant morbidity can also be a side effect of immunosuppression. Hypertension is the most frequently reported, occurring in approximately 40 per cent of pediatric transplant recipients mainly due to continued prednisone administration. Diuretics and antihypertensives, including captopril, enalapril, hydralazine, diltiazem, and nifedipine, are commonly used to control hypertension. Renal insufficiency due to cyclosporine use occurs in less than 5 per cent of children.[1] Another recognized side effect of cyclosporine therapy is gingival hyperplasia, which affects more than 70 per cent of patients. Gingival hyperplasia causes delayed and ectopic eruption of teeth, hampers speech development, and causes concern about cosmetic appearance.[58] Use of calcium channel blockers for hypertension and certain anticonvulsants for seizures can compound these effects. Post-transplantation diabetes mellitus (PTDM) is a well-known complication of tacrolimus-based immunosuppression in both adult and pediatric solid organ recipients.[59] Diabetes developed in 24 of 143 (17%) 30-day survivors of heart (12/96, 13%) and heart-lung/lung (12/47, 26%)

transplantation. In 17 (71%) patients, the immunosuppressive regimen at the onset of PTDM also included maintenance corticosteroids. Many patients require long-term insulin therapy for glucose control.

PROBLEMS SPECIFIC TO EACH ORGAN TRANSPLANT

Heart Transplant

Allograft Arteriopathy

Cardiac allograft vasculopathy (CAV), an unusually accelerated and diffuse form of obliterative coronary arteriosclerosis, is one of the major determinants of long-term outcome of the transplanted heart.[60] The disease presents with characteristic diffuse, concentric lesions of the coronary arteries, with myointimal proliferation, and disturbed internal elastic lamina affecting the muscular arteries of the graft. Often the penetrating myocardial arteries become occluded causing an infarct before the occlusion of the larger epicardial arteries.[60] Because the heart is denervated, these events are frequently asymptomatic until heart failure ensues. CAV seems to be due to a complicated interplay between immunologic and nonimmunologic factors resulting in repetitive vascular injury and a localized sustained inflammatory response. Immunosuppressive drugs, such as cyclosporine and corticosteroids, have been implicated in either directly or indirectly injuring the vasculature. In the immunocompromised patient, various organisms (viruses) may hasten the "nontransplant atherosclerosis" by simply damaging the vessels. Cytomegalovirus is particularly implicated as the inciting event in many patients. Other factors that may play a role are the immune system itself, dyslipidemia, and oxidant stress. It is claimed that the process occurs as a result of the chronic low-grade rejection/infectious process. Endothelial dysfunction is an early feature of CAV and progresses over time after transplantation.[60] Early identification of CAV is essential if long-term prognosis is to be improved. Annual coronary angiography is performed for diagnostic and surveillance purposes. Intravascular ultrasound is a more sensitive diagnostic tool for early disease stages and has revealed that progressive luminal narrowing in CAV is in part due to negative vascular remodeling. Because of the diffuse nature of CAV, percutaneous and surgical revascularization procedures have a limited role.[60] Prevention of CAV progression is a primary therapeutic goal.

Lung Transplant

Chronic Rejection

Chronic rejection usually occurs 6 months to 1 year after transplantation. It is characterized as graft dysfunction secondary to air-flow limitations. The target of the immune response in chronic rejection is the bronchial epithelium, manifested histologically as obliterative bronchiolitis. Airway injury stimulates fibroproliferation in the small airways, leading to narrowing and ultimately luminal obliteration. For diagnosis, transbronchial biopsy is necessary but has a low sensitivity.[61] Home spirometry helps detect a bronchiolitis syndrome (suggested by a sustained decrease in the FEV1 by 20 per cent upon consecutive measures)[62] and may do so before it is revealed by laboratory testing.[63] Similar to acute rejection, symptoms are nonspecific and include insidious onset of cough and dyspnea, although dyspnea is a later symptom and may portend more extensive disease.[64] Chest radiographic findings are nonspecific and may include volume loss, subsegmental atelectasis, linear opacities, and bronchiectasis.[65,66] The etiology of chronic rejection is obscure, but prior acute rejection,

Table 47.5: Graft and patient survival rate for heart transplant

Donor age	*3 months*	*1 year*	*3 years*	*5 years*
Graft survival	(%)	(%)	(%)	(%)
< 1 year	85.2	78.2	73.5	60.8
1-5 years	89.1	81.3	69.4	60.1
6-10 years	91.4	89.9	83.7	66.7
11-17 years	90.4	87.2	74.9	62.4
Patient survival				
< 1 year	86.5	80.2	73.8	62.7
1-5 years	90.5	83.5	72	69
6-10 years	89	87	84.3	71.5
11-17 years	91.1	88.3	79.6	66.5

Source: OPTN/SRTR data as on August 1, 2001. Cohorts are transplants performed during 1998-99 for 3 months and 1 year; 1996-97 for 3 years; and 1994-95 for 5 years survival.

cytomegalovirus infection, airway ischemia, and HLA mismatching have all been implicated.[67-70] In the majority of patients, the problem is difficult to resolve, and the mortality rate at 3 years after diagnosis high. Treatments may slow, but not terminate, functional decline.

Outcomes from Heart Transplants in Children

Graft and Patient Survival

Graft and patient survival rates for pediatric heart transplant recipients are shown in Table 47.5. Mortality is lower in those younger than 1 year of age (Table 47.4) and probably reflects the complexity of transplantation in the first year of life in children with complex congenital heart disease. Other factors that contribute to the lower mortality include failed surgical reconstruction, prolonged waiting time, severe cardiomyopathy, poor nutritional state and increased pulmonary vascular resistance. In spite of the decreased three-month survival in these youngest recipients, 72 per cent patient survival at five years (in a separate cohort) was actually somewhat higher than the other pediatric age groups. Thus, despite higher early postoperative mortality, late mortality appears to be lower, consistent with the possible immune advantage noted in young infants who undergo cardiac transplantation. Therefore, the long-term improved survival may reflect better graft acceptance with effective immunosuppression in this subgroup of patients. After the first year of age, there appears to be no significant difference in outcome at five years compared to other age groups.

Growth and Development

A major concern after pediatric transplantation is the impact of transplantation and immunosuppressive drugs on growth and development.[71] For cardiac transplant recipients, growth has been around the 25th per centile for normal individuals, for both weight and height. Steroids have been blamed for the poor growth seen previously in other solid organ transplant recipients. Most centers make every effort to wean their cardiac transplant recipients from steroids during the first year post-transplant. Heart transplantation, particularly in infants, can also have a negative effect on neurodevelopmental outcome. Patients less than 5 years of age had significantly lower IQ scores than did normal children, but their IQ scores did not differ from those in children who had undergone open heart surgery.[72] Using the Bayley Scale of Infant Development, Baum *et al* found that neuro-development was normal in 67 per cent, suspect in 10 per cent, and abnormal in 23 per cent.[73] Using the Psychomotor Development Index (PDI), a measure of gross motor skills used in posture and walking and running, and fine motor skills used in hand control, reach, and grasp, Baum *et al* showed that psychomotor development was normal in 67 per cent, suspect in 20 per cent, and abnormal in 13 per cent.[73]

Quality of Life

Quality of life in surviving children, as judged by activity, is usually "normal." Most recipients do not have activity limitation and do not require frequent hospitalizations. Despite the return to apparently normal play and school activity in 95 per cent of children,[1] exercise testing in pediatric transplant recipients indicates abnormal exercise capacity.[74,75] Leg fatigue was the usual reason for terminating exercise. Sedentary life style, poor body image, and depression all may contribute to exercise intolerance. Pharmacologic agents may also have indirect effects by inhibiting erythropoietin production, altering muscle metabolism, or reducing muscle strength.[39] Younger age at time of transplantation was found to relate to more normal exercise capacity, whereas pretransplantation clinical status, duration of heart failure before transplantation, and posttransplantation cardiac index had no effect.[75]

Psychologic Functioning

Emotional stability and positive psychologic functioning are critical to the success of transplantation, because emotional stability provides an environment conducive to consistent medication administration and medical follow-up. The earliest reports on quality of life describe improvement in children who, before undergoing transplantation, had been socially isolated and depressed, with low self-esteem related to physical limitations.[76] After undergoing transplantation these children were ambulatory, attended school regularly, and had age-appropriate friends and play activities. The experience of organ transplantation clearly affects the family and the function of children within the family. Positive family coping was linked to more effective coping by the children.[77] When these reports are taken as a whole, it can be concluded that undergoing transplantation improves the child's emotional status by making a more normal lifestyle possible, but some problems remain. The positive effect of transplantation can be enhanced by assisting families with stress and coping before and after transplantation.[78]

Outcomes from Lung Transplantation

Survival

These results are obtained from the Organ Procurement and Transplantation Network Annual Report.[2] Compared to adult recipients, lung graft survival is slightly higher at three months for recipients aged 6 to 10 years (90%) and 11 to 17 years (92%). Five-year graft survival rates in the pediatric population are similar to those for the older patients, varying from 27 to 50 per cent. The overall graft survival rate was 41 per cent in the entire lung transplant population. Patient survival, after lung transplantation in pediatric patients, appears to be similar to or slightly higher than in the adult population at five years. The five-year survival rate for patients aged less than one year at transplant was 33 per cent; in those aged 6 to 10 years the survival rate was 64 per cent. For recipients aged 11 to 17 years, 45 per cent of patients were alive at five years. Lung transplantation in the pediatric population continued to be an unusual procedure with graft and patient survival rates similar to those seen in the adult populations. Very young recipients may possess some shorter-term immune advantage; however, the age cut-off at which this and any improvement in longer-term outcome is noted is still unclear, given the small number of patients transplanted. Overall, patient survival rates of five years are significantly worse than for cardiac transplantation, again reflecting the complexity of lung transplant immunology and the late development of bronchiolitis obliterans in the majority of recipients.

Outcomes from Heart-lung Transplantation

Few meaningful data are available on graft survival at three months, one year, three years, and five years in pediatric heart-lung transplant recipients because of the small number of transplants done. One exception is among recipients aged 11 to 17 years. For these children, the five-year survival rate of 46 per cent is similar to the survival rate of the overall population. This suggests indirectly that there is no graft survival disadvantage for pediatric subgroups. As would be expected, patient survival largely mirrors graft survival. Again, the only meaningful data available are for recipients 11 to 17 years old, who have a five-year survival rate of 54 per cent. This is slightly better than the overall survival for the entire cohort (49%). Heart-lung transplantation continues to be an extremely rare procedure in the pediatric population. The limited indications for heart-lung transplantation, the use of lung transplantation for pulmonary diseases in preference to heart-lung transplant in most centers, and the significant limitation of donor organ availability have limited the use of this procedure. Overall survival rates, however, after heart-lung transplantation appear to be similar to those seen in lung transplantation in pediatric patients, although the very limited number of transplants make statistically valid comparisons difficult.[2]

Psychosocial Issues Before and After Transplantation

Psychosocial issues are critical for both the recipient and their families. Parents are called upon to make life-and-death decisions for their child, rather than for themselves. In a study of 24 parents of 15 children by Higgins and Kayser-Jones, the factors that influenced decision-making were a combination of familial (effect of personal goals, quality of life), social (personal circumstances, e.g., teenaged single parent), psychologic and emotional (factors eliciting a strong response), and physician endorsement.[79] Suddaby *et al* studied 26 parents of 18 children and found that 77 per cent of parents reported moderate levels of stress.[80] The most common stressors were the illness of the child or other family members, work problems, recent pregnancy, and intrafamily conflicts.[80] Parents of girls viewed transplantation more negatively than did the parents of boys.[80] There was also a correlation between stress and a negative perception of transplantation. Coping mechanisms identified were religious faith, accepting difficulties, and facing problems head-on. The family's adaptation before transplantation correlates with function after transplantation, including the number of repeated hospital admissions for the pediatric recipient.[81]

Important Differences between Adult and Pediatric Heart Transplants

In the adult population, the main indications are roughly equally split between cardiomyopathies and coronary artery disease, with a minority of patients having congenital heart disease. Survival is lower in the infant age group compared to the older age group; adolescents have the same survival rate as adults. Other differences include more severe organ shortage, non-availability of portable circulatory assist devices, and more technically difficult transplantation in infants and children. The daily activities of infants, children, adolescents and adults are considerably different from each other. Respiratory distress from a failing heart manifests itself as poor feeding, prolonged feeding times, severe tachypnea after feeding, and sweating during or after feeding in infants. Failure to thrive or retarded growth rate may be a sign of chronic heart failure. Other considerations must include the irreversibility of the disease process, availability of and response to alternative therapies, presence of comorbidities, and psychosocial readiness.

The ultimate goal of transplantation is donor-specific tolerance. Pediatric heart transplantation can represent a unique immunologic opportunity for organ transplantation because the development of the immune system extends not only into infancy, but continues throughout childhood and adolescence. Favorable graft tolerance induction in neonatal recipients is anticipated since the cellular, endocrine, and humoral components of the immune system mature postnatally in humans. Age-dependent changes in immune function are likely to play a role in graft survival, optimal induction, and immunosuppressive regimen, and may need to be changed in concert with maturation of the immune system.

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Section Three

Circulatory System

CHAPTER 48

Shock: Management of Shock in PICU

Praveen Khilnani

DEFINITIONS

Shock is one of the most dramatic and life threatening condition faced by pediatricians in critical care setting. Untreated shcok is universally lethal, with proper recognition, monitoring and treatment, the morbidity and mortality can be significantly reduced.

Shock can be defined as "acute circulatory failure" with inadequate or inappropriately distributed tissue perfusion resulting in generalized cellular hypoxia.[1] Shock is not a problem of blood pressure or blood volume, but whatever the underlying cause, it is always a problem of inadequate cellular sustenance.[2-4]

Discussion on sepsis and septic shock is set as Chapter 51. What follows is a general description of pediatric shock.

PATHOPHYSIOLOGY

Shock is a syndrome that results from inadequate oxygen delivery to meet metabolic demands:

$$DO_2 < VO_2$$

Untreated this leads to metabolic acidosis, organ dysfunction and death.

Oxygen Delivery

Oxygen delivery = Cardiac Output × Arterial Oxygen Content

$$(DO_2 = CO \times CaO_2)$$

Cardiac Output = Heart Rate × Stroke Volume

(CO = HR × SV) where SV (Stroke Volume) is determined by preload, afterload and contractility.

Arterial Oxygen Content = Oxygen Content of the RBC + the Oxygen Dissolved in Plasma

$$(CaO_2 = Hb \times SaO_2 \times 1.34 + (.003 \times PaO_2)$$

Delivery of oxygen is a direct function of the cardiac output and arterial oxygen content. Inadequate oxygen delivery can result from either limitation or maldistribution of blood flow.[5] Ocassionally increased oxygen requirements, (fever, sepsis) may result in cellular oxygen deficiency with normal blood flow and delivery. Reduced oxygen content (anemia, poor arterial oxygen saturation) requires higher cardiac output to maintain oxygen delivery.

The cardiovascular system is under complex neuro-endocrinal control designed to maintain an adequate delivery of oxygen and substance to the tissues. Cardiac output is the product of stroke volume (SV) and heart rate (HR). The stroke volume is the volume of blood ejected from heart per ejection cycle.

CO (ml/min) = SV (ml/beat) × HR (beats/min)

In infants and children, elevation of heart rate is the most important compensatory mechanism for increasing cardiac output. Children do not increase their stroke volume as much. Stroke volume is determined by preload, afterload and cardiac contractility.

Preload is determined by the volume of venous return to the heart. A decrease in circulating blood volume as in dehydration, haemorrhage, etc. results in decrease volume of venous return to the heart and decreased stroke volume and cardiac output. Volume resuscitation increases cardiac output by increasing venous return and preload.

Afterload is defined as the ventricular wall tension during systole. It is determined by the systematic vascular resistance. Increase in systematic vascular resistance or afterload causes and increase in work of heart and decrease in cardiac output.

Another determinant of stroke volume is myocardial contractility. Acidosis, hypoxia, toxins and sepsis, all these decrease contractility.

When oxygen delivery fails to meet the cellular oxygen demands, various compensatory mechanisms are activated that increase the heart rate and cause vasoconstriction with shunting of blood to more vital organs. Shock, therefore, is a dynamic process and the exact cardiorespiratory pattern clinically detected depends on the complex interaction of patients illness, time elapsed and treatment provided.[1-6]

PHASES OF SHOCK

Because of its progressive nature shock may be divided into three phases:

- Compensated (Normotensive)
- Uncompensated (Hypotensive)
- Irreversible.[7]

In compensated shock vital organ fuction is maintained primarily by intrinsic compensatory mechanisms. Previously healthy children can compensate extremely wellduring hypoperfusion states.[8] For this reason, early compensated stages of all types of shocks can be very difficult to differentiate from patients normal status.[6,8] Due to rapidity of change, identification of early compensated stage of shock is of paramount importance. Patient is normotensive but has tachycardia and poor capillary refill time.

In uncompensated state, microvascular perfusion becomes marginal despite compensatory mechanisms. Patient is hypotensive. Cellular function deteriorates and disturbance in function becomes evident in all organ systems.[8] Terminal or irreversible shock implies damage to key organs of such magnitude that death occurs even if therapy returns cardiovascular parameters to normal levels.

Compensatory Mechanisms

Renin-angiotensin system Decreased perfusion to the kidney leads to renin secretion. Renin is eventually converted to Angiotensin II leading to vasoconstriction and aldosterone release. Aldosterone leads to sodium and water reabsorption.

Humoral responses:

- Catecholamine release leading to increased contractility and
- Vasoconstriction.

Autotransfusion

- Reabsorption of interstitial fluid.

Clinical Presentation

Early diagnosis requires a high index of suspicion. Diagnosis is made through the physical examination focused on tissue perfusion. Hypotension is a late and primorbid sign, indicates decompensation.

CLASSIFICATION OF SHOCK

Shock states may be broadly classified into five functional categories. Any classification of shock must allow for various overlaps.

- *Hypovolemic* (Table 48.1) Vomiting, diarrhea, trauma, burns, blood loss.

Table 48.1: Hypovolemic shock—etiologies

Whole Blood Loss

- Hemorrhage—absolute loss
- External bleeding
- Internal bleeding
- Gastrointestinal
- Intra-abdominal (spleen, liver)
- Major vassel injury
- Intracranial (in infants)
- Fractures

Relative Loss

- Pharmacological (barbiturates, vasodilators)
- Positive—pressure ventilation
- Spinal cord injury
- Sepsis
- Anaphylaxis
- Plasma loss
- Burns
- Capillary leak syndromes
- Inflammation sepsis
- Anaphylaxis
- Protein—losing syndromes
- Nephrosis
- Intestinal disorders or obstruction

Fluid and Electrolyte Loss

- Vomitting and diarrhoea
- Excessive diuretic use
- Endocrine
- Adrenal insufficiency
- Diabetes insipidus
- Diabetic ketoacidosis

Table 48.2: Cardiogenic shock—etiologies

- Heart rate abnormalities
- Supraventricular tachycardia
- Ventricular dysrhythmias
- Bradycardia
- Cardiomyopathies/carditis
- Hypoxic and ischemic events
- Cardiac arrest
- Prolonged shock
- Head injury
- Anomalous coronary artery
- Excessive catecholamine states
- Metabolic
- Hypoglycemia
- Hypocalcemia
- Acidosis
- Thyroid disorders
- Hypothermia
- Glycogen storage disease
- Carnitine deficiency
- Mucopolysacchatidosis
- Infections
- Sepsis
- Myocarditis
- Vascular, immunological
- Kawasaki's disease
- Polyarteritis nodosa
- Systemic lupus erythematosus
- Embolism
- Acute rheumatic fever
- Drug intoxication
- Neuromuscular diseases
- Duchenne's dystrophy
- Friedreich's ataxia
- Miscellaneous
- Endocardial fibroelastosis
- Congenital heart disease
- Trauma

- *Cardiogenic* (Table 48.2) Myocarditis, cardiomyopathy, septic myocardial dysfunction
  - Dysrhythmia.
  - CHD-(duct dependant).
- *Obstructive* (pulmonary embolism, aortic/mitral stenosis, Pneumothorax, Tamponade, Dissection).
- *Distributive shock* (septic shock, neurogenic, anaphylactic).
- *Dissociative*
  - Heat, Carbon monoxide, Cyanide
  - Endocrine

Vicious cycles play a prominent role in most shock syndromes. Any patient, overtime, may display features of any functional category. In first three categories there is decrease in tissue perfusion and blood supply. In distributive shock, blood flow might be increased but there is maldistribution of blood flow.

Precise etiologic classification may be delayed. Immediate treatment is essential.Absolute or relative hypovolemia is usually present. The size of the cardiac silhouette on plain film can be used to estimate the need for volume replacement.

ASSESSMENT AND RECOGNITION OF SHOCK

To apply aggressive, life-saving therapeutic interventions, early recognition of shock or impending shock is crucial. Consistent vigilance is required to identify the early stage of shock and facilitate therapy. Because of the rapidity of change and possibility of catastrophic deterioration, early transfer to pediatric ICU is essential to allow intensive monitoring while diagnostic evaluation is continuing. The early diagnosis of shock requires high index of suspicion and a knowledge of various conditions predisposing children to shock. Age of the child might provide some diagnostic clues and previous medical conditions or history of trauma raises the suspicion that the child may be suffering from a state of shock. In children shock can also occur after surgery especially after cardiac surgey. Children who are febrile, have an identifiable source of infection or are hypovolemic from any cause are at great risk of developing shock. It may be very difficult to determine when children have progressed from being dehydrated and febrile to having fully developed shock.

Therefore, the recognition of states in which shock is likely to develop is more important that recognition and identification of shock states. Therapeutic interventions are indicated in these patients before they actually develop shock.

The most effective and sensitive physiological monitoring available is, repeated and careful physical examination by an experienced and competent observer. Because the shock can be rapidly fatal, the child must be assessed immediately and comprehensively by rapid cardiopulmonary assessment.

Rapid Cardiopulmonary Assessment: In a healthy child the cardiovascular system has remarkable compensatory capability, so there is generally a stability of blood pressure and only an increase in pulse until there is sudden decompensation which may lead to precipitous cardiac arrest.

In clinical examination one must note following points very carefully:

- *Mental status*: Restless, agitated, anxious, comatose.
- *Skin*: Temperature, color, turgor, presence of rash.
- *Mucus membranes*: Color, moistness.
- *Capillary refill time*: More than 2 seconds is abnormal.
- *Respiratory rate* and depth.
- *Heart rate*: Tachycardia.
- *Urine output:* Hourly.

By far, the most significant physical findings in shock results from autonomic responses to stress. In children *tachycardia* occurs early. The younger the child, cardiac output is more dependent on heart rate rather than on increase in stroke volume. Alteration in blood pressure is a late manifestation of hypovolemia in children. Blood pressure is well maintained initially and only begins to fall once hemodynamic compromise is severe. It is important to remember that physical findings will vary according to type of shock and more importantly to the stage of shock.

Laboratory Investigations

Further assessment of the severity and cause of shock is assisted by several laboratory investigations. Routine laboratory tests such as electrolytes, blood cell counts, c-reactive protein and hematocrit are necessary to find the extent of metabolic disturbances. Serum calcium should be measured in all shock states as hypocalcemia occurs frequently and can further compromise respiratory muscle, myocardial and metabolic functions.

Serum proteins, albumin and colloid oncotic pressure measurements serve as guides to volume replacement. Arterial blood gases measurement is most important in evaluation of the adequacy of ventilatory function that is frequently impaired in shock. Determination of pH and base deficit gives us most readily available method of quantifying tissue hypoperfusion. The degree of metabolic acidosis correlates with severity of tissue hypoperfusion and readily guides the adequacy of therapy.

Persistent acidosis indicates inadequate of ineffective therapy. Restoration of normal pulse and blood pressure but with persistent metabolic acidosis requires further action, monitoring and therapeutic support.

MONITORING OF SHOCK

Monitoring for children with shock is best done with admission to pediatric ICU. Minimum monitoring of child with shock includes continous ECG monitoring, frequent temperature recordings, blood pressure measurements and pulse oximetry. In younger infants blood glucose should be frequently monitored.Simple hypovolemic shock can probably be managed with minimal monitoring.

Reliance upon non-invasive means for accurate information and continous monitoring of blood pressure is remarkably unreliable. Intra-arterial cannulation allows continous beat to beat measurement and allows frequent blood gas sampling.

Central venous catheterization allows access to the central circulation for the purpose of monitoring of central venous pressure (CVP) and administering blood products large volume fluid replacement, vasocative and inotropic medications and parenteral nutritional support. CVP must be interpreted cautiously. The most important complication of CVP monitoring is an erroneous interpretation of significance of the value given.[8,9]

In very selected cases when the etiology of shock state or appropriateness of therapy is in doubt, pulmonary artery catheterization may help intensivist to obtain more complete data to regulate therapy. Though not frequently used in pediatric ICU measurement of total oxygen uptake and oxygen delivery may be of value. The measurement of mixed venous oxygen saturation (SvO_2) allows the calculation of both oxygen uptake and oxygen extraction or utilization.

TREATMENT OF SHOCK

The treatment of shock in children is aimed at optimizing perfusion of critical vascular beds and preventing or correcting metabolic abnormalities arising due to cellular hypoperfusion. The ultimate goals are to prevent or reverse the defects in cellular substrate delivery and metabolism and to support entire patient until homeostasis is restored. For all forms of shock, *treating the underlying cause is mandatory*. Speed is essential. Delays in making the diagnosis and initiating treatment, as well as suboptimal resuscitation, contribute to the developments of peripheral vascular failure and irreversible defects in oxygen use which can culminate in cital organ dysfunction.

Two major priorities in treatment of shock are:

- Rapid assessment of patient's disease process and
- Achievement of cardiopulmonary stability
- *VIP approach can be used in initial treatment of shock. V standing for ventilation, I for infusion and P for pumping or cardiovascular support.*

Initial resuscitation of child in shock involves assessment of airway, administration of oxygen and establishment of intravenous access.

Respiratory Support (Ventilation)

The first priority is to secure the airway. Ensure adequate oxygenation and ventilation. High flow oxygen system (e.g. Venturi masks) must be used. Oxygen supply is optimized by maintaining arterial oxygen saturation, by correcting anemia and by increasing cardiac output and systemic blood flow. If airway is unstable and adequate oxygenation and ventilation is not achieved, endotracheal intubation should be performed and mechanical ventilation initiated. Because mechanical ventilation abolishes or minimises work of breathing, reduces oxygen consumption and improves oxygenation, early respiratory support benefits patients with severe shock and those with cardiogenic shock complicated by pulmonary edema.

Cardiovascular Support

Tissue blood flow must be restored by achieving and maintaining an adequate cardiac output and by ensuring that systematic blood pressure is sufficient to maintain perfusion of vital organs. Cardiovascular support involves manipulation of heart rate and rhythm and of three determinants of stroke volume (preload, myocardial contactility and afterload).

Rate and Rhythm

Assuring adequate heart rate and rhythm is basic to life support. Monitoring of heart rate is essential in guiding therapy. It is important to keep in mind that heart rate varies according to age and heart rates are acceptable within a wide range of normal for age. Dysrhythmias must be speedily and adequately treated. That includes correction of hypoxia, acidosis, and electrolyte disturbances. Temporary pacing and cardioversion may be needed in certain situations.

Preload and Volume Replacement

Preload optimization is most efficient way of increasing cardiac output. Rapid intravascular volume expansion guided by repeated clinical examination and urine output is frequently adequate to restore blood pressure and peripheral prefusion. Pulmonary edema with volume overload is rare in pediatric patients. Volume replacement of 20 ml/kg can be safely given and repeated until clinical parameter such as blood pressure, heart rate, capillary refill show improvement as 60-80 ml/kg fluid as been given. Controversy continues about whether colloids or crystalloids are preferable.[10-12]

As a first resuscitation fluid crystalloids such as normal saline or Ringers loctate are cheap and readily available. Colloids such as plasma and blood are used after initial use of crystalloids. As well as being fundamental to the management of hypovolemic shock, replacement of circulating volume is important in managing patients with cardiogenic distributive or obstructive shock.

The absolute contraindication of preload augmentation in children is a persistent elevation in ventricular filling pressures without an increase in cardiac output. Further preload augmentation does no improve peripheral perfusion and by increasing venous pressure may increase vascular leak leading to increased tissue edema, most notably pulmonary edema as evident by rales, hepatomegaly.

Choice of Fluid for Volume Replacement[10-14]

Blood: Indicated in hemorrhagic shock and to maintain hemoglobin at around 10 gm in shock due to othe causes.

Crystalloids: Crystalloids are cheap, convenient to use and free of side-effects. Crystalloids are rapidly distributed across intravascular and interstitia spaces. With crystalloids volume 2-4 times of colloid required for same volume expansion, transien volume expansion. Colloids (starch, gelatins produce greater and more sustained increase in plasma volume. Colloids are expensive.

Albumin: Should be used only in special circumstances, e.g. burns. However a recent study from Africa showed albumin as a preferred fluid in malaria patients with shock.[15]

MYOCARDIAL CONTRACTILITY

Inotropic and Vasoactive Agents

Before cardiac output and perfusion pressure are restored with drugs, abnormalities that might impair cardiac performances should be corrected. Metabolic acidosis secondary to tissue hypoxia should be managed by treating the cause. Bicarbonate should be given only for severe acidosis that fails to respond to adequate resuscitation.

If signs of shock persist despite adequate volume replacement and perfusion of vital organs is jeopardized, Inotropic drugs may be used to improve cardiac output (See chapter 49).

The effects of particular drug in an individual patient are unpredictable and must be closely monitored. Drugs commonly used in pediatric ICU to increase myocardial contractility include following drugs:

Dopamine: It has alpha, beta and dopaminergic (delta) actions that are dose dependant. At low dosed (< 10 mcg/kg/min) it primarily causes weak renal and splanchnic vasodilation and positive myocardial inotropic effect. At higher doses (> 10 mcg/kg/min), it has string vasoconstricting alpha effect, in addition to positive inotropic effect so called 'Renal dose' of dopamine (2-5 microgram/kg/min) for renal vasolidation has been over emphasized and is of less practical significance in clinical setting. The primary indication for dopamine is the need to increase myocardial contractility after preload restoration. Usual dose is 5-20 microgram/kg/min titrated to desired effect. Dopamine should preferably, be given via central line.

Dobutamine: It is selective beta-1 agonist. It causes an increase in cardiac contractility and reduces peripheral resistance. The reduction in afterload and improved myocardial performance lowers ventricular filling pressures. Usual dose is 5 to 15 microgram/kg/min.

Adrenaline: It is an alpha and beta adrenergic agonist. It is used in situations where dominant hemodynamic feature is peripheral vascular failure as in septic shock. At higher doses severe vasoconstriction can lead to lactic acidosis and renal and splanchnic ischemia. The usual dose is 0.1 microgram/kg/min to 1 microgram/kg/min. It should be titrated closely and minimum dose should be used for required.

Norepinephrine: An alpha and beta agonist (alpha > beta effect). Cardiac contractility is increased but it also causes massive increase in myocardial oxygen consumption and afterload, so cardiac output may not actually increase. Usual dose is 0.05-1 g/kg/min.

Afterload Reduction

Afterload reduction plays a role in improving myocardial performance in children with cardiogenic shock after surgery, myocarditis, ischemic heart disease or in the later stages of septic shock with myocardial failure. Both nitroprusside and nitroglycerin lower systemic vascular resistance in children and are useful afterload reducing agents.[16,17] These agents act via generation of nitric oxide. Nitroprusside has potent peripheral arterial vasodilating effects. Nitroglycerin is more potent vasodilator and pulmonary vasodilator. Close monitoring and volume augmentation are frequently required when vasodilators are used to decrease pulmonary vascular resistance. When pediatric patients remain in a normotensive, low-cardiac-output, and high-vascular-resistance state, despite epinephrine and nitrosovasodilator therapy, the use of a phosphodiesterase inhibitor should be strongly considered, such as milrinone.

SUPPORTIVE THERAPY

The management of the multisystem deterioration with shock states is as important as treating the underlying condition. Renal, gastrointestinal, CNS and hematological abnormalities in shock need to be deligently searched for, identified and treated. Parental or enteral nutrition should begin as soon as cardiovascular stability is achieved. Early use of enteral feedings to prevent gut mucosal atrophy and bacterial translocation is recommended.

SUMMARY

An aggressive multimodality approach to the treatment of shock is required. Ensuring a patient airway, and adequate oxygenation is always first step. Preload augmentation with intravenous fluid therapy should rapidly follow and is most important therapy in nearly every instance. Frequently oxygen, ventilation and fluid therapy are all that is required and administration of pharmacologic agents is the final step in treatment of shock, however, aggressive use of inotropes to achieve supranormal oxygen delivery is no longer recommended. Adequate oxygenation of tissues is most important. Detailed management of cardiogenic shock and septic shock is discussed in separate chapters.

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CHAPTER

Inotropes and Vasopressors in the Pediatric Intensive Care Unit

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Inotropes and vasopressor agents are commonly used in the PICU setting for management of patients with shock unresponsive to fluid therapy, cardiogenic shock, postoperative congenital heart surgery with low cardiac out put setting.

Definitions

Inotrope: A chemical agent that improves the cardiac muscle contractility (Inotropy).

Vasopressor: A chemical agent that improves the peripheral vascular tone leading to increased peripheral vascular resistance and increase in arterial blood pressure.

Chronotropy: Agent that increases heart rate is termed chronotropic agent.

Lusotropy: Agent that increases cardiac compliance, inodilatation (diastolic myocardial muscle relaxation) is termed lusotropic agent.

Basis for Use of Inotropic Support

The circulation exists to provide the tissues with oxygen and nutrition and to remove the waste products. The cardiovascular system maintains a head of pressure and the other organs divert flow to serve its needs. We know that blood pressure depends on cardiac output and the resistance of the vessels into which the heart is pumping. A drop in either will decrease the mean pressure in the system. A variety of intravascular sensors exist which sense such a drop in pressure and the body compensates either by increasing the peripheral resistance or by increasing cardiac output. However, when there is a substantial drop in blood pressure the compensatory mechanism that maintains the blood pressure fails. If such a drop in blood pressure is large and sustained it may lead to the death of the patient. The main reason to administer inotropes is to prevent the deleterious side effects of hypotension in such patients. However, there are other patients who are also afflicted by the failure of heart to provide sufficient pressure to perfuse the organs which include loss of intravascular volume due to blood loss or fluid loss in such a condition the heart has little blood to pump.

Tables 49.1 and 49.2 show various abnormalities seen in physiological parameters in different types of shock and the physiological actions of various inotropes and vadopressors on the various sympathetic receptors of the autonomic nervous system.

One of the earliest inotropes mostly used in situations of poor cardiac performance (congestive cardiac failure) and for rhythm abnormalities such as atrial fibrillation, and tachycardic rhythms: Digoxin will be discussed in the following section, followed by the clinical pharmacology and practical use of various inotropes and vasopressors in the PICU.

DIGOXIN

A digitalis glycoside has been used in congestive cardiac failure for long time.[1,2]

Mechanism(s) of Action

Electrolyte changes occur with each heart beat (action potential).

Table 49.1: Physiological parameters in different types of shock

Type	*Heart rate*	*Stroke volume*	*Cardiac output*	*SVR*
Cardiogenic	Increased	Decreased	Decreased	Increased
Hypovolemic	Increase	No change or decreased	No change or decreased	Increased
Septic early	Increased	Increased	Increased	Decreased
Septic late	Increased	Decreased	Decreased	Increased
Spinal	Decreased or normal	No change	Decreased	Decreased

Table 49.2: Physiological receptor actions of various inotropes

	Receptor stimulation by various catecholamines					
	Alpha		Beta			
Agent	1	2	1	2	3	*Dopaminergic*
Adrenaline (epinephrine)	+++	+++	++	++	++	–
Noradrenaline (norepinephrine)	++	++	++	–	+++	–
Dobutamine	+ –	–	+++	+	?	–
Dopamine	++	++	++	+	?	+++

- At rest
  - Sodium is high outside
  - Potassium is high inside
  - *Free* calcium is low inside
- After the action potential goes through:
  - Sodium is higher inside
  - Potassium is lower inside
  - *Free* calcium is higher inside

Something has to put things back where they belong *after* the action potential. That *something* is the Na/K ATPase (actually many copies of this tiny pump per cell). Digoxin inhibits the Na/K ATPase pump slowing the depolarization of SA node and increases the refractory period of AV node.

- Positive inotropic effect
- Negative chronotropic effect of digoxin
- Stimulates vagus centrally
- Increases refractoriness of AV node
- Decreases ventricular response to atrial rate
- Controls heart rate in atrial fibrillation
- Slows depolarization rate of SA node
- Decreases sinus rate
- Decreases heart rate in sinus tachycardia
- Decreases sympathetic tone
- Contractility and stroke volume increase

It is potentially invaluable in patients with atrial fibrillation and coexistent heart failure, improving control of the ventricular rate and allowing more effective filling of the ventricle. Digoxin is also used in patients with chronic heart failure secondary to left ventricular systolic impairment, in sinus rhythm, who remain symptomatic despite optimal doses of diuretics and angiotensin converting enzyme inhibitors, where it acts as an inotrope.

Digoxin: Practical Aspects[1,2]

The Digitalis Investigation Group's large study found that digoxin was associated with improvement in the symptoms of patients with congestive heart failure, when added to treatment with diuretics and angiotensin converting enzyme inhibitors. Importantly, there were greater absolute and relative benefits in the patients who had resistant symptoms and more severe impairment of left ventricular systolic function. However, although there was a reduction in the combined end points of admission and mortality resulting from heart failure. Table 49.3 depicts comparative pharmacokinetics of various oral preparations of digoxin.

Table 49.3: Comparative pharmacokinetics of digoxin dose forms

	Tablets	Elixir	Capsules
Oral absorption	60%	80%	75-90%
Time to peak (min)	90	45-60	60-90

Maintenance dose is 10 microgram/kg daily. Reduced maintenance dose should be given, when renal impairment is present, and when used with drugs that increase digoxin concentrations (amiodarone, verapamil). Concentrations should be monitored, especially in cases of uncertainty about whether therapeutic levels have been achieved (range 6 hours after dose: 1.2-1.9 ng/ml). Potassium concentrations (avoid hypokalemia) and renal function should be monitored.

Adverse Effects

Digoxin toxicity may be associated with: (a) adverse symptoms (for example, nausea, vomiting, headache, confusion, visual symptoms); and (b) dysrhythmias (for example, atrioventricular junctional rhythms, atrial tachycardia, atrioventricular block, ventricular tachycardia). Serious toxicity should be treated by correcting potassium concentrations and with drugs such as Beta 2 blockers and glycoside binding agents (cholestyramine), and in severe cases by specific digoxin antibodies (Digibind).

THE CHOICE OF INOTROPES AND VASOPRESSORS

Following agents and their clinical pharmacology pertaining to the use in critically ill children will be discussed.

Dopamine
Dobutamine
Epinephrine
Milrinone
Norepinephrine
Vasopressin

DOPAMINE

Dopamine (3, 4 dihydroxyphenylethylamine) is the immediate precursor of norepinephrine and epinephrine; it is a central neurotransmitter particularly important in the regulation of movement and possesses important intrinsic pharmacological properties. Dopamine is a substrate for both MAO and COMT.

Clinical Pharmacology

Dopamine stimulates dopamine (D1 and D2) receptors located in the brain and in vascular beds in the kidney, mesentery and coronary arteries[1]. It also stimulates alpha and beta receptors, although the compounds affinity for these receptors is lower.

The predominant effects of dopamine are dose-related, although it should be noted that actual response of an individual patient would largely depend on the clinical status of the patient at the time the drug is administered. At low rates of infusion (0.5-2 mcg/kg/min) dopamine causes vasodilatation that is presumed to be due to a specific agonist action on D1 dopamine receptors in the renal, mesenteric, coronary, and intracerebral vascular beds. The vasodilatation in these vascular beds is accompanied by increased glomerular filtration rate, renal blood flow, sodium excretion, and urine flow.[2] Low dose infusion of dopamine has frequently been used to augment renal function in critical illness,[3] although evidence suggests that this method may increase the fractional excretion of sodium and the creatinine clearance,[4] a large randomized double blind placebo control study of low dose dopamine (2 mcg / kg/min) administered to critically ill patients at risk of renal failure did not show any benefits.[5]

At intermediate rates of infusion (2-10 mcg/kg/min) dopamine acts to stimulate the beta$_1$-adrenoceptors, resulting in improved myocardial contractility (positive inotropy), increased SA rate (positive chronotropic) and enhanced impulse conduction in the heart. There is little, if any, stimulation of the beta$_2$-adrenoceptors (peripheral vasodilatation). Dopamine causes less increase in myocardial oxygen consumption than isoproterenol, and its use is not usually associated with a tachyarrhythmia. Clinical studies indicate that it usually increases systolic and pulse pressure with either no effect or a slight increase in diastolic pressure. Blood flow to the peripheral vascular beds may decrease while mesenteric flow increases due to increased cardiac output. At low and intermediate doses, total peripheral resistance (which would be raised by alpha activity) is usually unchanged.

At higher rates of infusion (10-20 mcg/kg/min) there is some effect on alpha 1-adrenoceptors, with consequent vasoconstrictor effects and a rise in blood pressure. The vasoconstrictor effects are first seen in the skeletal muscle vascular beds, but with increasing doses, they are also evident in the renal and mesenteric vessels. At very high rates of infusion (above 20 mcg/kg/min), stimulation of alpha-adrenoceptors predominates and vasoconstriction may compromise the circulation of the limbs and override the dopaminergic effects of dopamine, reversing renal dilation and narituresis.

Therapeutic Use

Dopamine remains the mainstay of pharmacological support in shock. It is recommended as the first line agent for children with fluid refractory septic shock.[6] It may also be appropriate for children with mild impairment of myocardial function and hypotension after resuscitation from cardiac arrest.[7] Dopamine is also used in infants and children following cardiac surgery although it is less effective than dobutamine in that setting.[8]

Pharmacokinetics

Dopamine is ineffective when administered orally. Following intravenous administration the drug is widely distributed in the body but does not cross the blood-brain barrier to a significant extent. Dopamine is metabolized in the liver, kidney, and plasma by MAO and catechol-O-methyltransferase to the inactive compounds homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid. About 25 percent of the dose is taken up into specialized neurosecretory vesicles (the adrenergic nerve terminals), where it is hydroxylated to form norepinephrine. It has been reported that about 80 percent of the drug is excreted in the urine within 24 hours, primarily as HVA and its sulfate and glucuronide conjugates and as 3,4-dihydroxyphenylacetic acid. A very small portion is excreted unchanged. Plasma dopamine clearance ranges from 60- 80 ml/kg/min in normal adults. It is lower in renal and hepatic disease.

The elimination half-life of dopamine is approximately 2 mins.[9] It is higher in neonates and critically ill children, being 5 to 11 mins and 26 ± 14 mins respectively.[10] Clearance of dopamine in children younger than 2 yr is twice as rapid as in older children. There is a wide interindividual variation in the rate of its clearance.[11] Dopamine clearance may also decrease after 24 hours of continuous infusion. Differences in the rate of sulfoconjugation as a route of elimination may also contribute to the wide variations in the clearance of dopamine.

Preparation and Administration

DRIP Calculation: Rule of Six
6 × bodyweight in kg = mg to mix in 100 ml
1 ml/hr = 1 microgram/kg/min.

If fluid overload and drip volume needs to be reduced then double concentration (to run at half the infusion rate), or triple concentration (to run at one third the infusion rate) will provide the same calculated dose to be delivered.

Dopamine is available as 5 ml ampules in a concentration of 40 mg/ml. It is diluted in 5 percent dextrose or normal saline for administration. It is given as an infusion preferably through a central line. In an emergency, dopamine can be administered through an intraosseous needle. During the infusion, all patients require intermittent evaluation of blood volume and frequent assessment of myocardial function, perfusion of vital organs, and the production of urine. Most patients should receive intensive care, with monitoring of arterial and venous pressures and the ECG. Reduction in urine flow, tachycardia, and the development of arrhythmias may be indications to slow or terminate the infusion.

Adverse Effects and Contraindications

Before dopamine is administered to patients in shock, hypovolemia should be corrected by transfusion of whole blood, plasma, or other appropriate fluid. Untoward effects due to over dosage are generally attributable to excessive sympathomimetic activity. Nausea, vomiting, tachycardia, arrhythmias, headache, hypertension, and vasoconstriction may be encountered during an infusion of dopamine, although it is less likely to produce these side effects than epinephrine or isoproterenol. It increases myocardial oxygen demand by increasing cardiac oxygen consumption. Since the drug has an extremely short half-life in plasma, these effects usually disappear quickly if the infusion is slowed or interrupted. It decreases the ventilatory response to hypoxia and hypercarbia by almost 60 percent.[12] It has been shown to increase intrapulmonary shunting in ARDS by interfering with hypoxic vasoconstriction and decreasing PaO_2.[13] In postoperative cardiac infants, dopamine may decrease pulsatility of growth hormone, prolactin and thyrotropin levels.[14] Extravasation of large amounts of dopamine during infusion may cause ischemic necrosis and sloughing. Rarely, gangrene of the fingers or toes has followed the prolonged infusion of the drug. If this is threatened, local infiltration of the region with phentolamine should be instituted.[15]

Drug Interactions

Dopamine physically interacts with soda bicarbonate and calcium and should not be administered in the same line.

Dopamine should be avoided or used at a much reduced dosage (one-tenth or less) if the patient has received a MAO inhibitor. Careful adjustment of dosage also is necessary for the patient who is taking tricyclic antidepressants, as responses may be particularly variable. Dopamine antagonists such as metoclopramide or haloperidol may attenuate response to dopamine.

Dopexamine, is a newer agent not available in India. It Acts on beta 2 and D receptors. It increases cardiac output and reduces afterload. Increases blood supply to the kidneys and possibly also the gastrointestinal tract. There is paucity of pediatric data, however Adult data supports the use in lowcardiac output states.

Drip Dose is 0.5-6 mcg/kg/min.

DOBUTAMINE

Dobutamine is a synthetic catecholamine. It resembles dopamine structurally but possesses a bulky aromatic substituent on the amino group. The pharmacological effects of dobutamine are due to direct interactions with α and β adrenergic receptors.[1] Although dobutamine originally was thought to be a relatively selective β1 adrenergic agonist, it is now clear that its pharmacological effects are complex. Dobutamine possesses two enantiomeric forms are present in the racemic mixture that is used clinically.[2] The (–) isomer of dobutamine is a potent agonist at α1 receptors and is capable of causing marked pressor responses. In contrast, (+) dobutamine is a potent α1 adrenergic receptor antagonist, which can block the effects of (–) dobutamine. The (+) isomer is about ten times more potent as β adrenergic receptor agonist than is the (–) isomer but is nearly devoid of α agonist activity. In summary the dobutamine racemate and (–) dobutamine are potent partial α agonists.

Clinical Pharmacology

The cardiovascular effects of racemic dobutamine represent a composite of the distinct pharmacological properties of the (-) and (+) stereoisomers. Dobutamine has relatively more prominent inotropic than chronotropic effects on the heart compared to isoproterenol. Alternatively, cardiac β1 receptors may contribute to the inotropic effect. At equivalent inotropic doses, dobutamine enhances automaticity of the sinus node to a lesser extent than does isoproterenol; however, enhancement of atrioventricular and intraventricular conduction is similar for the two drugs.

In animals, administration of dobutamine at a rate of 2.5 to 15 microgram/kg/min increases cardiac contractility and cardiac output. Total peripheral resistance is not greatly affected. The relative constancy of peripheral resistance presumably reflects counterbalancing of α1 adrenergic receptor mediated vasoconstriction and β2 receptor-mediated vasodilatation. The heart rate increases only modestly when the rate of administration of dobutamine is maintained at less than 20 microgram/kg per minute.[3,4] After administration of β adrenergic blocking agents, infusion of dobutamine fails to increase cardiac output, but total peripheral resistance increases, confirming that dobutamine does have modest direct effects on α receptors in the vasculature.

Therapeutic Uses

Dobutamine has been used in a variety of conditions associated with poor myocardial function. Specific indications for dobutamine in children are those associated with low output CHF and normal to moderately decreased blood pressure. It is most commonly used in viral myocarditis, cadiomyopathy or myocardial infarct (Kawasaki's disease). Dobutamine increases cardiac output and stroke volume in such patients, usually without a marked increase in heart rate[5]. Alterations in blood pressure or peripheral resistance are usually minor, although some patients may have marked increases in blood pressure or heart rate. Clinical evidence of longer-term efficacy remains uncertain.

It has been found to be of use following corrective or palliative cardiovascular surgery when myocardial dysfunction is suspected or demonstrated. It is of particular use in children undergoing operation for mitral valve disease.[6] it is not the first line of treatment for low output states caused by intra-cardiac shunts or abnormal cardiac structure.[7]

Septic Shock

Dobutamine is useful when there is impaired myocardial performance. It is used when ventricular dysfunction becomes an important complicating factor. In combination with dopamine it has been shown to increase cardiac output, left ventricular stroke volume and blood pressure.[8]

Pharmacokinetics

Dobutamine is always given as a continuous infusion, usually in the range of 5 to 20 microgram/kg/min. The onset of effect is rapid. Consequently, a loading dose is not required, and steady-state concentrations generally are achieved within 10 minutes of initiation of an infusion. The rate and duration of the infusion are determined by the clinical and hemodynamic responses of the patient.

Dobutamine has a half-life of about 2 minutes.[9] An apparent volume of distribution of dobutamine is estimated to be 0.2 L/kg and total body clearance is 2.33 L/min/m^2. Dobutamine is metabolized by liver mainly by catechol-O- methyl transferase (COMT) to 3-O-methyldobutamine, with subsequent conjugation to glucuronic acid, and excretion in the urine and bile (Some dobutamine is excreted as dobutamine glucuronide). Both major metabolites are pharmacologically inactive.

Clearance of dobutamine from the circulation is first-order. An enormous variation in dobutamine levels is noted at similar infusion rates. For example, at 5 mcg/kg/min, serum concentrations of the drug range from 25 to 350 ng/ml, a fourteen-fold variation. In addition, clearance changes substantially with time in individual patients. Such variation can be explained if one considers the hepatic metabolism of the drug, and that even in normal individuals there is a five-fold variation in hepatic COMT content from person to person. It is thought that after more than 72 hours of dobutamine usage, tolerance occurs to the effects of the drug. This may be due to beta-receptor down-regulation.

Preparation and Administration

DRIP Calculation: Rule of Six
6 × bodyweight in kg = mg to mix in 100 ml
1 ml/hr = 1 microgram/kg/min

If fluid overload and drip volume needs to be reduced then double concentration (to run at half the infusion rate), or triple concentration (to run at one third the infusion rate) will provide the same calculated dose to be delivered.

Adverse Effects

In some patients, blood pressure and heart rate may increase significantly during administration of dobutamine; this may require reduction of the rate of infusion. Patients with a history of hypertension may be at greater risk of developing an exaggerated pressor response. Since dobutamine facilitates atrioventricular conduction, patients with atrial fibrillation are at risk of marked increases in ventricular response rates. Some patients may develop ventricular ectopic activity. Dobutamine increases myocardial oxygen demand. The efficacy of dobutamine over a period of more than a few days is uncertain; there is evidence for the development of tolerance. It is less likely to produce atrial and ventricular arrthymias than other catecholamines but may do so in patients of myocarditis, electrolyte imbalance and high infusion rates.[8] It should be administered with caution in dynamic LV outflow obstruction. Prolonged infusions have been reported to inhibit platelet aggregation.

Drug Interactions

Very few drug interactions have been reported with dobutamine. It may increase insulin requirement in diabetics.[9]

EPINEPHRINE

Epinephrine is a potent stimulator of both α and β adrenergic receptors, and its effects on target organs are thus complex. It is synthesized in the adrenal medulla and is the principal hormone of stress.

Clinical Pharmacology

Epinephrine has widespread metabolic and haemodynamic effects. Particularly prominent are its actions on the heart and on vascular and other smooth muscles.

Cardiac Effects

Epinephrine is a powerful cardiac stimulant. It acts directly on the predominant β1 receptors of the myocardium and of the cells of the pacemaker and conducting tissues. The force of contraction of myocardium is increased by the positive inotropic action and the heart rate increases by positive chronotropic action. The myocardial oxygen consumption increases out of proportion to the increase in force of contraction, decreasing the myocardial efficiency[1].

Blood Pressure

Epinephrine is one of the most potent vasopressor drugs known. It evokes a characteristic effect on blood pressure, which rises rapidly to a peak that is proportionate to the dose on rapid IV injection. The increase in systolic pressure is greater than the increase in diastolic pressure, so that the pulse pressure increases. These effects are mediated via different mechanisms, myocardial stimulation and increase in the heart rate through β1 receptors and vasoconstriction in many vascular beds, specially in the pre-capillary vessels of skin mucosa and kidney through a receptors.

Small doses of epinephrine promote relaxation of resistance arterioles through stimulation of β2 receptors causing the diastolic blood pressure to fall. At slightly higher rates of infusion, there may be no change or a slight rise in peripheral resistance and diastolic pressure, depending on the dose and the resultant ratio of α to β2 responses in the various vascular beds; compensatory reflexes also may come into play. Pulmonary vascular resistance also increases at higher doses from direct effect of epinephrine and secondary to increased venous return.

Vascular Effects

The chief vascular action of epinephrine is exerted on smaller vessels and precapillary arterioles. Various vascular beds react differently which results in a substantial re-distribution of blood flow. Cutaneous vasoconstriction occurs via α receptors. Blood flow to skeletal muscles is increased in therapeutic doses due to powerful β2 receptor vasodilator action. In usual doses, there is no significant constrictor action on cerebral arterioles. Doses of epinephrine that have little effect on mean arterial pressure consistently increase renal vascular resistance and reduce renal blood flow by as much as 40 percent [1]. Arterial and venous pulmonary pressures are raised. Although direct pulmonary vasoconstriction occurs, redistribution of blood from the systemic to the pulmonary circulation, due to constriction of the more powerful musculature in the systemic great veins, plays an important part in the increase in pulmonary pressure. Very high concentrations of epinephrine may cause pulmonary edema precipitated by elevated pulmonary capillary filtration pressure and possibly by "leaky" capillaries.

Effects on Smooth Muscles

The effects of epinephrine on the smooth muscles of different organs and systems depend on the type of adrenergic receptor in the muscle. Gastrointestinal smooth muscle is, in general, relaxed by epinephrine. This effect is due to activation of both α to β2 adrenergic receptors. Intestinal tone and the frequency and amplitude of spontaneous contractions are reduced. Stomach usually is relaxed and the pyloric and ileocecal sphincters are constricted, but these effects depend on the preexisting tone of the muscle. If tone is already high, epinephrine causes relaxation contraction.

Epinephrine relaxes the detrusor muscle of the bladder as a result of activation of β2 receptors and contracts the trigone and sphincter muscles owing to its α agonist activity. This can result in hesitancy in urination and may contribute to retention of urine in the bladder.

Respiratory Effects

It has a potent bronchodilator action most evident when bronchial muscle is contracted because of disease, as in bronchial asthma. It also inhibits mast cell degranulation via β2 receptors and decreases bronchial secretions and mucosal congestion by a receptor stimulation.

Metabolic Effects

Epinephrine has a number of important influences on metabolic processes. It elevates the concentrations of glucose and lactate in blood. Insulin secretion is inhibited through an interaction with α receptors and is enhanced by activation of β2 receptors; the predominant effect seen with epinephrine is inhibition.[1] It also increases plasma free fatty acids by stimulating β2 receptors in adipose tissue.

Therapeutic Use

Epinephrine is used to treat dopamine unresponsive "cold shock".[2] At modest infusion rates (0.05 -0.1 μg/kg/min), SVR decreases slightly and heart rate, cardiac output and systolic blood pressure increase. In adults with septic shock, it has been shown to increase cardiac output, stroke volume and oxygen delivery.[3] At very high doses (> 1- 2 μg/kg/min) α1 adrenergic mediated vasoconstriction comes into play causing increase in afterload and thereby impairing myocardial function.

Epinephrine is also used for cardiogenic shock unresponsive to dopamine or following cardiac surgery.[4] It is also the agent of choice for hypotension following successful resuscitation of cardiac arrest.

Pharmacokinetics

Epinephrine is not effective after oral administration because it is rapidly conjugated and oxidized in the gastrointestinal mucosa and liver. Absorption from subcutaneous tissues occurs slowly because of local vasoconstriction, but is more rapid after intramuscular injection. Epinephrine is rapidly inactivated in the body by the liver and kidneys, which are rich in the enzymes responsible for destroying circulating epinephrine (COMT and MAO). The elimination half-life is approximately 1 minute.[5] There is a wide inter individual variation in epinephrine clearance in adults and in critically ill children.[6]

Preparation and Administration

DRIP Calculation: Rule of Six
0.6 × bodyweight in kg = mg to mix in 100 ml
1 ml/hr = 0.1 microgram/kg/min.

If fluid overload and drip volume needs to be reduced then double concentration (to run at half the infusion rate), or triple concentration (to run at one third the infusion rate) will provide the same calculated dose to be delivered.

Epinephrine is available in a variety of formulations geared for different clinical indications and routes of administration such as by injection, by inhalation, or topically. Epinephrine is unstable in alkaline solution and when exposed to air or light, turns pink from oxidation to adrenochrome and then brown from formation of polymers. Epinephrine injection is available in 1: 1,000 and 1: 10,000 solutions. When used as a pressor, it is administered as an infusion after diluting in dextrose or saline. The usual dose given is 0.1 to 1 μg/kg/min. The response is titrated to the desired blood pressure level. Serious side effects such as renal failure and arrhythmias should be closely monitored for.

Adverse Effects

Central Nervous System

Epinephrine may cause acute CNS reactions such as fear, anxiety, restlessness, throbbing headache, tremors and weakness.[1] The use of large doses or the rapid intravenous injection of epinephrine may result in cerebral hemorrhage from the sharp rise in blood pressure.

Cardiovascular System

Enhanced automaticity and increased oxygen consumption are the main serious toxicities. Epinephrine produces tachycardia. Higher infusion rates predispose to atrial and ventricular extrasystoles, ventricular tachycardia and ultimately ventricular fibrillation. These are more commonly seen with myocarditis, hypokalemia or hypoxia.

Manifestations of overdose in neonates include tachycardia, hypertension, cerebral hemorrhage, seizures and renal failures.[7] Rapidly acting vasodilators such as sodium nitroprusside can counteract the marked pressor effects of large doses of epinephrine.

Metabolic Effects

Epinephrine produces hypokalemia as a result of stimulation of beta 2 adrenergic receptors.[8] Infusion of 0.1 µg/kg/min lowers serum potassium by 0.8 mEq/L. Hyperglycemia results from beta-adrenergic mediated suppression of insulin release.

Drug Interactions

Tricyclic antidepressants potentiate the effects of epinephrine.[1] Epinephrine should not be used with fluorinated anesthetics because it increases the risk of ventricular arrhythmias.[9] Beta adrenergric blockers should not be administered while on epinephrine as it causes unopposed α1 activity leading to severe hypertension and cerebral hemorrhage.

MILRINONE

Traditionally, catecholamines such as dopamine, dobutamine, epinephrine, and norepinephrine have been used for their positive inotropic effect in children with low cardiac output. These agents, however, produce several undesirable effects, including an increase in heart rate and myocardial oxygen consumption and an increase in systemic vascular resistance. Unlike the catecholamines, milrinone produces a positive inotropic effect with concurrent vasodilation and little chronotropic effect. As a result of these differences, milrinone has become a valuable tool in the treatment of children following cardiac surgery and in the management of shock.

Mechanism of Action

Milrinone, like its predecessor inamrinone (formerly called amrinone), is a bipyridine inotrope and vasodilator. It is about 30 times as potent as amrinone. It is a selective inhibitor of peak cyclic adenosine monophosphate (cAMP) phosphodiesterase III[1] in cardiac and vascular muscle. Inhibition of this enzyme results in an accumulation of cAMP, producing an increase in intracellular ionized calcium in cardiac muscle, which increases contractile force. Increasing cAMP also produces relaxation of vascular smooth muscle. Milrinone exhibits a concentration-dependent response, with optimal effects occurring between 100 and 300 ng/ml. In addition it has been postulated that a portion of milrinone's action is mediated via inhibition of guanine nucleotide binding protein.[2] The anti-inflammatory capability of milrinone has been explored, offering another potential mechanism of clinical efficacy.[3]

Clinical Pharmacology

Milrinone causes improvement in cardiac function due to positive inotropic effect as well as a reduction of afterload and preload secondary to its vasodilator action.[1,4] When used in CHF it results in an increase in cardiac output and a reduction in SVR. Heart rate is not much affected. This causes an improvement in ratio of myocardial oxygen delivery to consumption. It decreases pulmonary vascular resistance in children with intracardiac left to right shunts.

Therapeutic Use

Use After Cardiac Surgery

Several investigators have studied the effects of milrinone in reversing the low cardiac output frequently observed in infants and children after cardiac surgery. Administration of milrinone has been shown to produce a significant increase in cardiac index, with a decrease in mean atrial pressure. Systemic vascular resistance and pulmonary vascular resistance decreases. Myocardial oxygen consumption is unchanged.[5,6] Since publication of these initial reports, milrinone has gained acceptance as an alternative or supplement to catecholamines in the management of pediatric patients with low cardiac output following repair of congenital heart defects. Although the data available to date have been promising, questions about the optimal timing for initiation of therapy, dosing, and monitoring remain. A prospective multicenter, randomized, double-blind, placebo-controlled study is currently under development to address these questions. The Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics (PRIMACORP) study will compare a low-dose milrinone regimen consisting of a 25 mcg/kg loading dose followed by an infusion of 0.25 mcg/kg/min, a high-dose regimen with a 75 mcg/kg loading dose followed by an infusion of 0.75 mcg/kg/min, and placebo for up to 36 hours.

Use in Septic Shock

In addition to its use after cardiac surgery, milrinone may also be beneficial in the management of low cardiac output resulting from septic shock. It is particularly useful in the setting of normal to low cardiac output with elevated SVR. In a prospective, double blind trial,[7] milrinone significantly increased cardiac index, stroke volume index and oxygen delivery while decreasing systemic vascular resistance, pulmonary vascular resistance, and mean pulmonary artery pressure. No significant changes were noted in heart rate, systolic or diastolic blood pressure, mean systemic arterial pressure, or pulmonary capillary wedge pressure.

Use in CHF

Milrinone has been used extensively in adults to treat CHF. It has been shown to cause a much greater decrease in left and right ventricular filling pressures and SVR than does dobutamine, even at equivalent contractility dosing.[8] Milrinone produces a greater reduction in SVR for a given degree of improvement in inotropic state as compared to dobutamine. Blood pressure is well maintained, inspite of reduced SVR, because of the associated improvement in contractility and stroke volume.

Pharmacokinetics

In adults, milrinone has a volume of distribution of 0.3 to 0.4 L/kg, a terminal elimination halflife of 1.5-2.3 hours, and a clearance of approximately 2 ml/kg/min. It is approximately 70 percent bound to plasma proteins at plasma concentration of 70-400 ng/ml.[9]

The primary route of excretion of milrinone in man is via the urine, with much smaller amounts recovered in the feces. The major urinary excretion products in man are milrinone (83%) and its 0-glucuronide metabolite (12%). Elimination in normal subjects via the urine is rapid, with approximately 60 percent recovered within the first 2 hours following dosing, and approximately 90 percent recovered within the first 8 hours following dosing. The mean renal clearance of milrinone is approximately 0.3 L/min while that of the metabolites is even greater, indicative of active secretion.

In patients with moderate to severe renal impairment, doses have to be adjusted. The half-life of milrinone increases from 0.94 hours in subjects with normal renal function to 1.71 hours in patients with moderate renal impairment and 3.09 hours in patients with severe renal impairment.

The pharmacokinetics of milrinone is altered in infants and children. In infants and young children undergoing cardiac surgery, the weight adjusted clearance of milrinone increases with age, ranging from 2.6 ml/kg/min at 3 months to 5.6 ml/kg/min at 22 months of age.[10] These studies also suggest that a larger loading dose, and perhaps a greater initial infusion rate, may be necessary in children to achieve serum concentrations within the desired range and produce an optimal cardiovascular response.[11]

Preparation and Administration

Milrinone is available as a clear pale yellow solution containing 1 mg/ml of milrinone. It is diluted to a maximum concentration of 200 mcg/ml in either saline or 5 percent dextrose for administration.. During therapy with milrinone, blood pressure and heart rate should be monitored and rate of infusion slowed or stopped in patients showing hypotension. Fluid and electrolyte changes and renal function should be carefully monitored during therapy with milrinone. Since a major part of milrinone is excreted unchanged in urine. Milrinone therapy is usually initiated with a loading dose followed by a continuous infusion.

Dose

A loading dose of 50 mcg (10 microgram/kg as a general guideline) is used in children[6] followed by maintenance infusion rates of 0.35–1 mcg/kg/min with a minimum target serum concentration of 100 ng/ml. The infusion rate is titrated according to the clinical response.

Adverse Effects

As with other positive inotropes, the phosphodiesterase inhibitors have the potential to produce arrhythmias. Milrinone produces a slight shortening of atrioventricular node conduction time, which may result in an increased ventricular response rate in patients with atrial flutter or fibrillation. In Phase II and III clinical trials of adults, ventricular arrhythmias were reported in 12 percent of patients. In these patients, 8.5 percent experienced ventricular ectopic activity, 2.8 percent had nonsustained ventricular tachycardia, 1 percent had sustained ventricular tachycardia, and 0.2 percent had ventricular fibrillation. Supraventricular arrhythmias occurred in 3.8 percent of patient. Hypokalemia has been reported in 0.6 percent of patients receiving milrinone and may predispose them to the development of arrhythmias. Other adverse effects associated with milrinone use in adult clinical trials include: hypotension (2.9%) seen most often with rapid administration of the loading dose, headaches (2.9%), angina (1.2%), tremor (0.4%), and thrombocytopenia (0.4%). The incidence of thrombocytopenia is substantially less than that seen with in amrinone (2.4%). Although pediatric studies are limited, the side effect profile of milrinone in children appears to be similar to adults. Milrinone should not be used in lieu of surgical relief of the obstruction in patients with severe obstructive aortic or pulmonic valvular disease. Like other inotropic agents, it may aggravate outflow tract obstruction in hypertrophic subaortic stenosis.

Drug Interactions

Milrinone is compatible with many other drugs commonly used in the intensive care setting. Milrinone should not be infused with furosemide. A chemical interaction occurs between these drugs resulting in formation of a precipitate. Mixing of milrinone and imipenem-cilastatin results in a change in the color of the solution from light to dark yellow. While the clinical significance of this color change has not been assessed, it may indicate drug inactivation.

NOREPINEPHRINE

Norepinephrine is the principal chemical mediator of postganglionic adrenergic nerves. It differs from epinephrine only by lacking the methyl substitution in the amino group. Norepinephrine constitutes 10 to 20 percent of the catecholamine content of human adrenal medulla.

Clinical Pharmacology

The pharmacological actions of norepinephrine and epinephrine have been extensively compared *in vivo* and *in vitro*. Their actions differ mainly in the ratio of their effectiveness in stimulating α and β2 receptors. They are approximately equipotent in stimulating β1 receptors. Norepinephrine is a potent agonist at *alpha* receptors and has relatively little action on β2 receptors; however, it is somewhat less potent than epinephrine on the *alpha* receptors of most organs.[1]

Cardiovascular effects. Norepinephrine increases systolic and diastolic pressures as well as the pulse pressure. Cardiac output is unchanged, and total peripheral resistance is raised. Compensatory vagal reflex activity causes bradycardia, and stroke volume is increased. The peripheral vascular resistance increases in most vascular beds, and blood flow is reduced to kidney, liver, and, usually, skeletal muscle[1]. Marked venoconstriction contributes to increased total peripheral resistance. Glomerular filtration rate is maintained unless the decrease in renal blood flow is very marked. Norepinephrine constricts mesenteric vessels and reduces splanchnic and hepatic blood flow. Coronary flow is substantially increased; probably owing both to indirectly induced coronary dilation, as with epinephrine, and to elevated blood pressure. Unlike epinephrine, small doses of norepinephrine do not cause vasodilatation or lower blood pressure, since the blood vessels of skeletal muscle constrict rather than dilate.

Norepinephrine is not as effective a "hormone" as epinephrine. The drug causes hyperglycemia and other metabolic effects similar to those produced by epinephrine, but these are observed only in large doses.

Therapeutic Use

Norepinephrine has a role in improving perfusion in children with low blood pressure and a normal or raised cardiac index. The most common scenario for its use includes septic shock. It is administered only after volume repletion and is best guided by the estimates of cardiac output and systemic vascular resistance. There is sufficient adult data providing a rationale for its use in patients with hypotension unresponsive to fluid resuscitation and dopamine.[2,3] In children, norepinephrine is recommended for warm shock refractory to volume repletion and dopamine.[4] Other causes of distributive shock also respond to norepinephrine when predominant hemodynamic problem is low systemic vascular resistance and low blood pressure.

The lowest infusion rates that improve perfusion are judged by skin color, temperature and mental status. Decreasing urine output and rising lactate levels should be viewed with caution indicating severe vasoconstriction. The usual recommended doses are 0.1- 1 mcg/kg/min. The titration of dose is important. It produces an increase in blood pressure, systemic vascular resistance. It is particularly useful in tachycardic individuals as it lowers heart rate through reflex vagal stimulation. Norepinephrine has been shown to improve right ventricular performance in adults with hyperdynamic septic shock.[5]

Pharmacokinetics

Norepinephrine, like epinephrine, is ineffective when given orally and is absorbed poorly from sites of subcutaneous injection. Basal plasma levels of norepinephrine are much higher than epinephrine levels. The clearance in healthy adults is 24 to 40 ml/kg/min with the half-life of 2-2.5 mins.[6] It is rapidly inactivated in the body by reuptake into nerve terminals with some elimination occurring by enzymatic degradation in the liver, adrenal glands and kidneys either by methylation (by COMT) or by oxidative deamination.[7] Small amounts normally are found in the urine. The excretion rate may be greatly increased in patients with pheochromocytoma.

Preparation and Administration

DRIP Calculation: Rule of Six
0.6 × bodyweight in kg = mg to mix in 100 ml
1 ml/hr = 0.1 microgram/kg/min

If fluid overload and drip volume needs to be reduced then double concentration (to run at half the infusion rate), or triple concentration (to run at one third the infusion rate) will provide the same calculated dose to be delivered.

Norepinephrine is available as 4 ml ampules in a concentration of 1 mg/ml. It is administered as an infusion after dilution with saline or 5 percent dextrose by a syringe infusion pump. The usual dose of administration is 0.05 to 1 mcg/kg/min. It is titrated to the desired effect with a close watch on the adverse effects.

Adverse Effects

The adverse effects of norepinephrine are similar to those of epinephrine, but they are usually less pronounced and less frequent. Anxiety, respiratory difficulty, and transient headache are the most common effects. Conventional doses in hypersensitive persons (*e.g.*, hyperthyroid patients) cause severe hypertension with violent headache, photophobia, stabbing retrosternal pain, pallor, intense sweating, and vomiting. The risk of cardiac arrhythmias contraindicates the use of the drug during anesthesia with agents that sensitize the automatic tissue of the heart. Norepinephrine should also not be given to patients with mesenteric or peripheral vascular thrombosis due to the risk of increasing ischemia.

Care must be taken that necrosis and sloughing do not occur at the site of intravenous injection owing to extravasation of the drug. The infusion should be made high in the limb, preferably through a long plastic cannula extending centrally. Infiltrating the area with phentolamine, an α receptor antagonist, may relieve impaired circulation at injection sites, with or without extravasation of norepinephrine[8]. Blood pressure must be determined frequently during the infusion and particularly during adjustment of the rate of the infusion. Blood pressure should not be raised above normotensive levels. Reduced blood flow to vital areas is a constant danger with the use of norepinephrine.

Drug Interactions

Tricyclic antidepressants potentiate the action of norepinephrine by reducing neuronal uptake of compounds. Alpha adrenergic blocking agents reduce its efficacy.

VASOPRESSIN

Vasopressin (VP) better known as antidiuretic hormone is a nonapeptide synthesized in hypothalamus and released from posterior pituitary gland.[1] It is an important hormone from the point of view of maintaining cardiovascular homeostasis in the body. It has been used for long time in patients of central diabetes insipidus and also in patients with variceal bleed but its vasopressor properties are now under review to be exploited in certain critical illness.

Clinical Pharmacology

Vasopressin is an endogenous hormone produced in the parvocellular and magnocellular neurons within the supraoptic and paraventricular nuclei of the hypothalamus. It is stored and released by the posterior pituitary gland in response to increases in plasma osmolality or as a baroreflex response to decreases in blood pressure and/or blood volume. Hypovolemia and shock are one the most potent non-osmotic stimuli for release of vasopressin.[2] The threshold for release in response to hypovolemia or hypotension is much higher than that of hyperosmolality; with decreases of more than 20 percent being required. However once the threshold is reached, plasma levels rise 20 to 30 fold, far exceeding those seen with hyperosmolality.[3]

The normal fasting blood level of VP is 4 pg/ml, a concentration enough for its action on renal collecting ducts.[1,4] But its vasopressor effects require a much higher serum concentration (about 10-200 pg/ml).[4] In early phase of shock its plasma level may reach > 100 pg/ml but levels come down later and may be inappropriately low in prolonged septic shock.[5,6]

Actions of VP are mediated via its three receptor subtypes designated as V1 (V1R/V1a), V2 (V2R) and V3 (V1b).[1,2] V1 vascular receptors are located on vascular smooth muscle and mediate vasoconstriction. Additionally, V1 receptors are found in the kidney, myometrium, bladder, adipocytes, hepatocytes, platelets, spleen, and testis. V1-receptor activation mediates vasoconstriction by receptor-coupled activation of phospholipase C and release of Ca++ from intracellular stores via the phosphoinositide cascade.[7,8]

V2 renal receptors (V2R), which cause the antidiuretic effects of vasopressin, are present in the renal collecting duct system and endothelial cells. Kidney V2 receptors interact with adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) and cause retention of water.[9] V3 pituitary receptors (formerly known as V1b) have central effects, such as increasing adrenocorticotropic hormone (ACTH) production, activating different G proteins, and increasing intracellular cAMP.[10] VP also acts on oxytocin receptor which is important from the point of view of its vasodilator action on certain vital organs through nitric oxide (NO) mediated pathway. Blood flow within the coronaries, as well as the cerebral, pulmonary, and renal vascular beds, ispreserved, promoting shunting to those areas. This regional vasodilation is likely the result of a complex interplay of vasopressin activity at V1 and endothelial V3 and oxytocin receptor sites producing an increase in nitric oxide release. In addition to these direct effects, vasopressin may also enhance or restore catecholamine sensitivity.

Synthetic vasopressin (8-arginine vasopressin) acts at the same receptor sites as endogenous vasopressin, producing an identical physiologic response.[1,11] Terlipressin is a long acting analogue of vasopressin that has been shown to have higher affinity for vascular receptors than vasopressin and has demonstrated potent vasopressor effects in adult patients with norepinephrine resistant septic shock.[12]

Clinical Use

Vasopressin is now emerging as a rational therapy in the management of septic shock and vasodilatory shock (systemic inflammatory response syndrome [SIRS] with hypotension) from other causes. It is primarily used in catecholamine resistant vasodilatory shock.

Most form of shock like states cause high levels of vasopressin levels in the body. But hemorrhage and septic shock cause biphasic changes in vasopressin concentrations, high concentrations in early shock, which decreases as the shock state progresses. It has been observed by Landry *et al*[6] and also corroborated in other studies as well.[5,13] Probable reason for this VP deficiency is depletion of neurohypophyseal stores after prolonged stimulation. Apart from this, autonomic insufficiency which leads to impaired release of VP and elevated endogenous NO and norepinephrine levels that have a central inhibitory effect on vasopressin release have also been implicated for its low level in this condition.

Many patients of septic shock show poor response to conventional catecholamine, probably related to receptor down regulation, and increased NO level and activation of K+ ATP channels in blood vessel smooth muscle cells.[4,5] In contrast septic shock patients are exquisitely sensitive to low dose vasopressin.[5,13,14] In many studies VP infusion in the dose of 0.01-0.04 U/min resulted in improved mean arterial pressure and permitted withdrawal of catecholamines.[5,13,15,16] Apart from this it has also been found to improve urine output. Although pediatric studies are few, its benefit has been demonstrated even in children.[17-20] Recently reports with the use of terlipressin have also been published.[21-23] Although vasopressin has shown promise in treatment of advanced vasodilatory shock, there are still no randomized controlled proving its efficacy. Further trials will be needed to standardize the exact timing and dose for its use in such situations.

Pharmacokinetics

Because vasopressin is destroyed by gastric trypsin, it must be administered parenterally.

Vasopressin is rapidly degraded by enzymes in the liver and kidneys, with elimination half-life of approximately 10 to 35 minutes.[1,11] Renal insufficiency and hepatic failure prolong its half-life.

Dosing, Preparation and Administration

Vasopressin is available as a 20-unit/ml injection. For continuous intravenous infusion, it should be diluted with normal saline or 5 percent dextrose to a final concentration of 0.1 to 1 unit/ml. Administration through central venous access is recommended to minimize the risk of extravasation. Although the stability of vasopressin infusions with other drugs has not been studied, a recent report on bolus vasopressin administration found it to be compatible with most of the drugs used commonly in the ICU.

Studies of vasopressin in adults with vasodilatory shock have used infusion rates of 0.01 to 0.1 units/min. In pediatric patients, a vasopressin dose of 0.3 to 2 milliunits/kg/min (equivalent to 0.0003 to 0.002 units/kg/min or 0.01 to 0.12 units/kg/hr) is recommended, based on the report by Rosenzweig.[17] The infusion should be titrated to optimize blood pressure and perfusion. It has been suggested that vasopressin infusions may be tapered over a 2 to 3 hour period, once blood pressure and the doses of concomitant catecholamine infusions are stabilized.

Drug Interactions

The vasoconstrictive effects of vasopressin are counteracted by vasodilators such as nitroglycerin or nitroprusside. The antidiuretic effect of vasopressin is increased by concomitant administration of carbamazepine chlorpropamide, fludrocortisone, and tricyclic antidepressants. The antidiuretic effect of vasopressin may be reduced by concurrent use of demeclocycline, heparin or lithium.

Adverse Effects

High dose vasopressin administration has been associated with hypertension, bradycardia, arrhythmias, and myocardial infarction. These adverse effects have been reported most frequently in patients with cardiovascular disease. Administration of vasopressin without adequate fluid resuscitation may also result in significant ischemia of other organs, including the gastrointestinal tract and kidneys. The development of ischemic skin and mucous membrane lesions is a known complication of vasopressin therapy; resulting from the intense vasoconstriction produced within the capillaries.[24] Ischemic lesions have been estimated to occur in as many as 10 to 30 percent of patients receiving low-dose vasopressin infusions. Extravasation of vasopressin from an

Table 49.4: Selecting inotropic and vasopressor agents for specific hemodynamic disturbances in children

	Blood pressure or SVR		
Hemodynamic pattern	*Normal*	*Deceased*	*Elevated*
Septic shock			
Stroke index high	None or dopamine	Norepinephrine	None
Stroke index low to N	Dobutamine or dopamine	Dopamine or epinephrine (or dobutamine plus norephinephrine)	Dobutamine plus nitroprusside
Cardiogenic shock	Dobutamine or milrinone or dopamine	Epinephrine or dopamine	
Myocardial dysfunction (complicating critical illness)	Dobutamine or dopamine or milrinone	Epinephrine or dopamine (or dobutamine plus norepinephrine)	Dobutamine plus nitroprusside
CHF	Dobutamine or dopamine or milrinone		Dobutamine plus nitroprusside
Bradycardia	None	Isoproterenol	None

infusion site can also produce intense local vasoconstriction, which may result in severe tissue necrosis and gangrene. The skin, particularly around the site of infusion, should be closely inspected on a regular basis to identify any signs of decreased perfusion.

Other adverse effects associated with vasopressin include: venous thrombosis, tremor, vertigo, sweating, hyponatremia, urticaria, abdominal cramps, vomiting and bronchial constriction. Hypersensitivity reactions, including anaphylaxis, have also been reported. Because of the ability of vasopressin to rapidly increase extracellular water content, it should be used with caution in patients with chronic nephritis and congestive heart failure.

SUMMARY

Practical approach to the patient who may require inotropes (see Table 49.4)

Drip dose calculation (rule of six)

Dopamine, dobutamine

6 mg/kg body weight in 100 ml : 1 ml/hr = 1 microgram/kg/min

Epinephrine, Norepinephrine

0.6 mg/kg body weight in 100 ml : 1 ml/hr = 0.1 microgram/kg/min.

Guideline

1. Aggressively sustain the blood pressure.
2. Assess the patient rapidly and thoroughly.
3. Ensure adequate volume status (CVP8-12).
4. Consider the administration of a small bolus of inotrope.
5. Wean the inotropes as rapidly as you can.

The assessment of response to inotropic support is undertaken utilizing a few clinical pointers:

1. Improvement in blood pressures
2. Improvement in thermoregulation
3. Increased urine output
4. Increased oxygenation
5. Decreased base deficit and lactate
6. Shift of mixed venous concentration towards normal
7. The core-peripheral temperature gradient narrows
8. Cardiac output returns to normal
9. Patient looks better.

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CHAPTER

50

Cardiogenic Shock

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The presentation of a neonate with hypotension, poor perfusion and depressed neurologic status is a medical emergency. Under these circumstances *resuscitation precedes diagnosis.*

Following discussion concentrates on the recognition, etiology and treatment of cardiogenic shock with a special emphasis on neonatal age group.

Cardiogenic shock implies primary failure of the heart as a pump. This occurs infrequently in the neonate, but the most common etiologies include: (i) congenital heart disease with reduced cardiac output and systemic hypotension; (ii) cardiac muscle disorders; (iii) dysrhythmias; and (iv)metabolic conditions. Hypovolemia and septic shock can present in a similar fashion.[1,2]

CLINICAL FINDINGS

There is usually little spontaneous movement in the infant with cardiogenic shock. Arterial pulses are thready or nonpalpable, capillary refill time is markedly increased and the blood pressure measurement is low. The skin has a mottled bluewhite or gray appearance. There is usually marked enlargement of the liver and crackles (rales) may be found on pulmonary auscultation. Usually, tachycardia is present although in advanced cases, bradycardia may be found. Several other findings that indicate pump failure include: (i) elevated systemic venous pressure compared with low venous pressure with septic or hypovolemic shock; (ii) presence of gallop rhythm; (iii) cardiomegaly on chest X-ray; and (iv) low voltage QRS complexes and ST-T changes on ECG. Simulators of cardiogenic shock include bilateral pneumothoraces, congenital lobar emphysema, hemorrhagic shock from ruptured spleen, septic shock from group *B Streptococcus* and pericardial tamponade from pneumoperricardium.

INITIAL TREATMENT

Upon presentation of a patient with cardiogenic shock with respiratory distress, supplemental oxygen should be administered. Endotracheal intubation and assisted ventilation should be initiated in order to decrease the work of breathing and prevent further decompensation and acidosis. ECG electrodes should be placed to immediately evaluate for complete heart block, ventricular and supraventricular dysrhythmia, long QT syndrome and to monitor heart rate. Both peripheral and central venous access should be obtained as well as arterial access for obtaining blood gas samples and for central venous pressure (CVP) and intra-arterial blood pressure monitoring. Vasoactive drugs should never be administered through arterial lines. Blood should be obtained for immediate dextrostix (random blood sugar) and sent for CBC, bacterial studies, electrolytes, glucose, type and cross-match. Central venous pressure measurements can help differentiate between septic or hemorrhagic shock and cardiogenic shock. Low pressures (less than 3 cm H_2O) are more common with septic or hemorrhagic shock and indicate need for possibly large volumes (50-75 ml/kg) of fluids. Measurements greater than 10 cm are consistent with cardiogenic shock and indicate need for the intravenous inotropic agents. Central venous pressure greater than 15 cm H_2O is indicative of pericardial tamponade or worsening cardiac failure. Arterial blood samples should also be obtained as soon as possible, so severe metabolic acidosis can be partially corrected with sodium bicarbonate. Inotropic agents are less effective in an acidotic milieu, so partial correction is essential. Lowering $PaCO_2$, by hyperventilation may also be used to aid in the correction of metabolic acidosis if a ductal dependent right to left shunting is not present. If, however, a right to left ductal lesion is present, lowering $PaCO_2$ by hyperventilation will only exacerbate an already congested pulmonary system by further lowering pulmonary artery resistance and thus further increasing pulmonary artery blood flow in this particular situation, increasing FiO_2 in an effort to raise PaO_2 is also detrimental as this will precipitate ductal constriction.

A chest and abdominal radiograph should be obtained to exclude pneumothorax, pneumopericardium or peritonitis. A lumbar puncture and blood cultures are indicated if there is a possibility of sepsis or meningitis. Once cultures are obtained, antibiotics should be administered for 48-72 hours until cultures are reported to be negative.

If it is possible that a ductal dependent lesion is present, then prostaglandin (PGE1) should be given (0.1 microgram/kg/min by continuous infusion) even prior to accurate diagnosis (Table 50.1). Initial agent of choice for bradycardia in the newborn is epinephrine (0.1 ml/kg of a 1:10,000 solution); other than the newborn age group, one could use epinephrine or atropine intravenously (0.01 mg/kg). Persistent bradycardia usually responds to isoproterenol 0.051.0 microgram/kg/minute. In infants with a high central venous pressure and high heart rate, dobutamine and/or dopamine may be used in dosages of 5-20 microgram/kg/minute. Frequently dobutamine is begun at a dose of 10 microgram/kg/minute in conjunction with dopamine at a dosage of 5-10 µg/kg/minute. Those children who remain bradycardic following treatment with appropriate inotropic agents are candidates for transvenous pacing. This is usually easily performed from a femoral approach.

Patients unresponsive to these support measures are candidates for possible corticosteroids (dexamethasone or hydrocortisone) use. The use of corticosteroids in the treatment of viral myocarditis remains controversial. This topic will be discussed further.

Table 50.1: Top five diagnoses presenting at different ages

Age on admission	*0 to 6 days (n = 1603)*
D-TGA	15%
HLH	12%
TOF	8%
COARCTATION	7%
VSD	6%
Other	52%
Age on admission	*7-13 days (n = 311)*
COARCTATION	20%
VSD	14%
HLH	9%
D-TGA	8%
TOF	7%
Other	42%
Age on admission	*14-28 days (n = 306)*
VSD	18%
TOF	17%
COARCTATION	12%
D-TGA	10%
PDA	5%
Other	38%

D-TGA = D-transposition of great arteries; HLH = hypoplastic left heart syndrome; TOF=tetralogy of Fallot; VSD = ventricular septal defect; PDA = patent ductus arteriosus. *Source:* DC Fyler and P Lang Neonatal. *Heart Disease.* In GB Avery (Ed). Neonatalogy: Pathophysiology and Management of the Newborn. Philadelphia Lippincott 1981.

SPECIFIC CONDITIONS

Congenital Heart Disease in the Neonate

Left Heart Obstructive Lesions

Although many different forms of congenital disease are capable of causing low cardiac output and systemic hypotension, the most common group of lesions which present in this fashion are those involving left heart obstruction. These include the hypoplastic left heart syndrome, critical aortic stenosis, coarctation syndrome, and interruption of the aortic arch. These lesions present usually within the first 1-2 weeks of life. The signs and symptoms are most often those of left atrial obstruction or left ventricular failure and varying degrees of cyanosis. Depending upon the level of the obstruction, pulses are either universally diminished or in the case of coarctation, a right arm and right leg differential may be detected. The degree of pulse discrepancy depends upon the patency of the ductus arteriosus as well as the degree of pulmonary hypertension. These children are usually tachypneic, tachycardiac, and apathetic with poor peripheral perfusion. The precordium is usually quite active, the second heart sound is either single or narrowly split, and an increased intensity should be appreciated. The chest X-ray usually shows a mildly enlarged heart with pulmonary venous engorgement. The ECG usually shows right ventricular hypertrophy with diminished left ventricular forces, especially in the case of hypoplastic left heart syndrome. Arterial blood gases may indicate only mild hypoxemia with PaO_2 in the 50-60 mm Hg range. The pH is usually normal until the onset of ductal closure, and the associated hypoxemia and hypoperfusion leading to severe metabolic acidosis. For this entire group of lesions, the definitive diagnosis can usually be made by echocardiography performed by a well-trained echocardiographer and modern equipment. Although their anatomy differs greatly and their potential surgical corrections as well as prognosis vary, the initial presentation and treatment are quite similar. Initial therapy includes initiation of PGE1 to reopen the ductus arteriosus, correction of hypoglycemia and acidosis if present and, in most cases, endotracheal intubation to control $PaCO_2$. This last item is very important in the management of these lesions as hyperventilation will further aid in lowering the pulmonary vascular resistance and worsen the overall hypoperfusion state by lessening the degree of right to left shunting through the patent ductus arteriosus. In most cases, we accept moderate hypoxemia to avoid hypoperfusion associated with more vigorous ventilatory management.

Anomalous Origin of the Left Coronary Artery from the Pulmonary Artery (ALCAPA)

This is a rare form of congenital heart disease occurring in approximately 0.4 percent of children with heart disease. This defect is frequently not recognized in the neonatal period; however, signs of cardiac dysfunction become apparent between 2 and 4 months of age, and may present as cardiogenic shock or left ventricular failure. In these infants, the blood supply to the left ventricle is dependent on anastomosis between the right and left coronary artery systems and the pulmonary artery pressure. During the neonatal period, the pulmonary artery pressure may be elevated and coronary perfusion is preserved. However, as pulmonary artery pressure decreases, a left to right shunt occurs from the right coronary artery via collateral vessels into the left coronary artery and into the pulmonary artery. This left to right shunt compromises the coronary capillary filling pressure and myocardial ischemia develops. Once again, the major signs and symptoms are those related to congestive heart failure, i.e. tachypnea. diaphoresis, and failure to thrive. Occasionally, the infants have paroxysmal attacks of acute discomfort precipitated by feeding which may be caused by myocardial ischemia. Examination of the heart frequently reveals an apical pansystolic murmur of mitral regurgitation secondary to papillary muscle infarction. The chest film usually shows cardiomegaly secondary to left ventricular and left atrial dilatation. The ECG typically shows evidence of myocardial infarction.

In some cases, definitive diagnosis may be made by two dimensional echocardiography with visualization of the anomalous artery from the pulmonary trunk. Doppler and color flow mapping modalities may also aid in the diagnosis by revealing bidirectional flow in the main pulmonary artery. In most cases, however, angiography performed in the ascending aorta is necessary to confirm the diagnosis.

Initial management of the infant involves medical treatment of congestive heart failure with digoxin and diuretics. In those infants with moderate to severe mitral regurgitation, treatment with afterload reducing agents such as captopril may be beneficial. Prolonged survival of these infants is possible with medical management alone, although more commonly we anastomose the left coronary artery to the ascending aorta either by mobilization and reimplantatian or by placement of a graft, if mobilization is not possible.[3,4]

Cardiac Muscle Disorders

Myocardial Asphyxia

Acute primary failure of the heart as a pump with no structural heart disease, dysrhythmia or metabolic disturbance is most often seen following intrapartum asphyxia. This entity may produce a clinical spectrum of cardiac disorders in the newborn, ranging from transient tricuspid insufficiency to serious combined ventricular failure with systemic hypotension and pulmonary arterial hypertension (cardiogenic shock). Tricuspid valve regurgitation with right ventricular volume overload and right ventricular failure appears to be secondary to papillary muscle ischemia or infarction as reflected by elevated levels of creatine kinase musclebrain (MB) fraction.[5,6] Sometimes there is mitral valve dysfunction also. Right ventricular failure after a seemingly mild prenatal and postnatal course can be associated with cyanosis, tachypnea and evidence of heart failure during the first 24 hours of life. In these infants, it appears this disorder is one of impaired coronary perfusion to portions of the ventricular myocardium through increased work demands created by unusually severe pulmonary vasoconstriction from initial hypoxemia. Left ventricular failure with systemic hypertension appears to follow asphyxia of a moderately severe degree. The elevation of systemic blood pressure is thought to be the result of adrenergic stimulation. Left ventricular failure associated with systemic hypotension appears to be a time related phenomenon. The progression from hypertension to hypotension appears to be related to the fact that fetal myocardial stores of norepinephrine are limited.[7]

In the case of severe hypoxemia related to cardiogenic shock in the newborn, the history is usually that of severe fetal distress with late and variable decelerations, meconium passage prior to delivery and fetal scalp blood pH between 6.9 and 7.1. Typically within the first hour, there is evidence of reduced systolic and diastolic pressures as well as elevated central venous pressures. Myocardial dysfunction is usually manifested by evidence of respiratory distress, hepatomegaly, gallop rhythm and markedly decreased heart rate variability. Less commonly there are ECG changes, ST depression and t-wave changes suggestive of myocardial ischemia. Other asphyxiated infants may show mild systemic arterial hypotension with evidence of pulmonary arterial hypertension, but without increased central venous pressure. In this case, it has been suggested that hypoxemia induced left ventricular dysfunction may play a role in persiste pulmonary hypertension of the newborn. Aft endotracheal intubation, restoration of ventilati and oxygenation as well as correction hypoglycemia and/or hypocalcemia, many infan will improve spontaneously without the use cardioactive agents. Other infants require single multiple cardioactive medications, and an occasion infant appears to sustain long-term myocardi damage with evidence of endocardial fibroelastosi In addition to routine respiratory care, digoxin an diuretics, attention has been directed to the use catecholamine and vasodilator agents.[8] F premature infants with hypotension and elevate central venous pressure. Cabal[9] and associates use a continuous infusion of isoproterenol with rapi improvement in the clinical condition and revers of abnormal findings within 36 hours. For ter infants with hypotension, Leitner[10] used lowdos dopamine (2.5 μg/kg/minute). If the system vascular resistance is increased (usually wit systemic hypertension), then vasodilators such sodium nitroprusside (0.5-0.10 microgram/kg minute) may be tried.

Myocarditis

Neonatal myocarditis may be caused by either vira bacterial, or protozoan agents. Viral myocarditis the most common with most of the responsib viruses from coxsackie B group. Other virus documented to cause neonatal myocarditis includ ECHO virus, Rubella virus, and Herpes. Bacteri myocarditis may occur with neonatal pneumonia an meningitis. The neonate who develops myocardit typically appears normal at birth. However, sig and symptoms of congestive heart failure quick develop and are recognizable as early as three da of life. Frequently, a history of viral infection in th mother during the last two weeks of pregnan provides a clue to the nature of the illness. Affecte infants are typically pale with diminished pulses, an capillary refill is generally poor. There is usually gallop rhythm with no significant murmur. The bloo pressure may vary from normal to significantly lo Chest X-ray film usually shows marked cardi enlargement and pulmonary venous congestion. Th ECG has diminished QRS voltage in the limb lead and t-wave inversion in the lateral precordial lead

Blood cultures should be drawn to rule out a bacterial cause. Congenital viral or protozoal infection may be suspected if there is microcephaly, microphthalmia, or chorioretinitis.

Once again, echocardiography helps to both confirm the clinical diagnosis as well as to exclude structural heart disease. Thus, there is typically left ventricular and left arterial enlargement with poor left ventricular contractility. Neonatal viral myocarditis has high morbidity and mortality. The heart failure in these infants is severe and frequently both ventilatory and inotropic support are required. During the acute phase, the management includes dobutamine at 10 microgram/kg/minute in conjunction with intermediate doses of dopamine 5-10 microgram/kg/minute. Milrinone is good inotropic agent with afterload reduction in normotensive patient. In hypotensive patient epinephrine may be added as a rescue measure. Digitalis may be administered during recovery phase; however, initial loading doses in 24 hours should not exceed 25-30 µg/kg because both supraventricular as well as ventricular dysrhythmias are common and may be exacerbated. ACE inhibitors may be added (such as Enalapril). The use of steroids during acute viral infections remain controversial because of the concern that they may promote viral replication and myocardial necrosis. It has been our policy to use steroids for myocarditis after five to seven days of illness in order to decrease the inflammation and help prevent the development of fibrosis. Immunosuppressive agents have been used to treat myocarditis in animals and humans; improvements in cardiac function and deceased in myocardial infiltrates were thought to occur.[11,12]

Intravenous immunoglobulins in the dose of 1 gm/kg /day may be given over four to five days. Single dose (2 gm/kg) has been shown to improve ventricular function and one year survival. Newer agents such as Levosimendan and Neseritide have shown promise in preliminary data.

Dysrhythmias

A more elaborate discussion of Pediatric dysrhythmias is discussed elsewhere, but the presence of supraventricilar and ventricular dysrhythmias must always be detected and treated with top priority.

Metabolic Causes

Hypoglycemia

Severe hypoglycemia has become much less common since the introduction of routine dextrostix screen for hypoglycemia in the newborn. Severe untreated hypoglycemia in the neonate, however, can be associated with significantly myocardial dysfunction as the newborn myocardium is almost exclusively glucose dependent.

Adrenal Insufficiency

This has been reported as a cause of cardiovascular collapse in the newborn. Diagnostic clues include increased levels of serum potassium as well as decreased levels of serum sodium.

Rare metabolic disorders that affect the cardiac muscle and cardiac muscle metabolism include pyruvate dehydrogenase deficiency, myotonic dystrophy, and possibly a carnitine deficiency. Although ventricular failure secondary to HIV (Human Immunodeficiency Virus) is uncommon in the newborn, this potential etiology should also be considered.

Miscellaneous Causes of Cardiac Failure

Aneurism of vein of galen or an arteriovenous fistula in a neonate could present as high output cardiac failure presenting with respiratory distress and metabolic acidosis, a bruit over the head may be strongly suggestive of such a condition.

Babys born with hydrops fetalis are in severe cardiac failure due to severe anemia secondary to ABO/Rh incompatibility.

Other rare causes such as cardiac tumors leading to left ventricular outlet obstruction leading to sudden cardiovascular collapse.

SUMMARY

The neonate with circulatory failure and cardiogenic shock is a difficult management problem. However, the initial approach is that of resuscitation with exact diagnosis of secondary concern. Once the infant has been stabilized and septic and hypovolemic shock have been excluded, attention should be directed to the four most likely causes of cardiogenic shock: structural heart disease with left heart obstruction being the most common, cardiac muscle disorders. Cardiac dysrhythmias, and cardiac metabolic disorders. Other noncardiac causes such as arteriovenous malformations should be kept in mind. In addition, Simulators of cardiogenic shock as previously mentioned include bilateral pneumothoraces, congenital lobar emphysema, hemorrhagic shock from ruptured spleen, septic shock from group *B streptococcus* and pericardial tamponade from pneumopericardium.

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CHAPTER

Pediatric Septic Shock

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INTRODUCTION

According to WHO 2006 data, pneumonia, diarrhea, neonatal sepsis are top on the list of killers of children.

Consensus definitions of sepsis were first published[1] and later updated in a consensus conference.[2] Better understanding of pathophysiology, new interventions and better use fo existing therapies in the past decade included the publication of surviving sepsis campaign guidelines[3] recently revised.[4] In 2002 Carcillo et al published American College of Critical Care Medicine Clinical Guidelines for hemodynamic support of neonates and children with septic shock.[5] These guidelines were widely disseminated through the Society of Critical Care Medicine (SCCM) and the American Heart Association (AHA), as well as translated into Spanish and Portugese. These guidelines have been tested and the outcomes published by many centers.[6-9]

One institution that put guidelines into practice reported improvement in outcomes 1-3 percent in previously healthy and 7-10 percent in chronically ill children,[10] in line with best practice outcomes as targeted by the guidelines.

At the World Federation of Pediatric Intensive Care and Critical Care Society (WFPICC) Congress in Geneva June 2007, Dr Carcillo emphasized the importance of simple things such as early fluid therapy, early antibiotics, oxygen by nasal cannula, vasopressors by peripheral intravenous (IV) access to achieve a goal directed therapy can potentially avoid further deterioration and improve outcomes.

In the following discussion consensus definitions of sepsis and rapid cardiopulmonary assessment will be described followed by essential elements of pediatric sepsis management.

For pathology reader is referred to several publications.

DEFINITIONS

Following are the definitions published in 2005(2), related to sepsis and septic shock. Table 51.1 shows age-specific ranges for physiologic and laboratory variables.

A. SIRS (Systemic Inflammatory Response Syndrome)

The presence of at least two of the following four criteria, one of which must be abnormal temperature or leukocyte count:

1. Core temperature of >38.5°C (Core temperature must be measured by rectal, bladder, oral or central catheter probe).
2. Tachycardia, defined as a mean heart rate > 2 SD above normal for age in the absence of external stimulus, chronic drugs, or painful stimuli; or otherwise unexplained persistent elevation over a 0.5 to 4 hours time period.

   Or

   For children <1 year old: bradycardia, defined as a mean heart rate <10th percentile for age in the absence of external vagal stimulus, beta-blocker drugs, or congenital heart disease; or otherwise unexplained persistent depression over a 0.5 hour time period.

Table 51.1: Age-specific vital signs and laboratory values

Age group	Heart rate (Tachycardia)	Heart rate (Bradycardia)	Respiratory rate (Breaths/min)	Leukocyte count (×1000/cu m)	SBP
0-1	>180	<100	>50	>34	<65
1 wk - 1 mo	>180	<100	>40	>19.5 or<5	<75
1 mo - 1 yr	>180	<90	>34	>17.5 or <5	<100
2-5 yr	>140	NA	>22	>15.5 or <6	<94
6-12 yrs	>130	NA	>18	>13.5 or <4.5	<105
13-< 18 yrs	>110	NA	>14	>11or <4.5	<117

Lower values for heart rate, leukocyte count, SBP (systolic blood pressure) are for the 5th percentile and upper values for heart rate, respiratory rate or leukocyte count for the 95th percentile

3. Mean respiratory rate > 2 SD above normal for age or mechanical ventilation for an acute process not related to underlying neuromuscular disease or the receipt of general anesthesia.
4. Leukocyte count elevated or depressed for age (not secondary to chemotherapy-induced leucopenia) or > 10 percent immature neutrophils.

B. Infection

A suspected or proven (by positive culture, tissue stain, or polymerase chain reaction test) infection caused by any pathogen or a clinical syndrome associated with a high probability of infection. Evidence of infection includes positive findings on clinical examination, imaging, or laboratory tests (e.g. white blood cells in a normally sterile body fluid, perforated viscus, chest radiograph consistent with pneumonia, petechial or pupuric fulminans).

C. Sepsis

SIRS in the presence of or as a result of suspected or proven infection.

D. Severe Sepsis

Sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions. Organ dysfunctions are defined in Table 51.2.

E. Septic Shock

Sepsis and cardiovascular organ dysfunction as defined in Table 51.2.

The detection of altered organ function in the acutely ill patient constitutes multiple organ dysfunction syndrome (two or more organs involvement). The terminology dysfunction identifies this process as a phenomenon in which organ function is not capable of maintaining homeostasis. This process, which may be absolute or relative, can be more readily identified as continuum of change over time.

Rapid Cardiopulmonary Assessment and Clinical Examination of a Patient in Shock

Because the shock can be rapidly fatal the child must be assessed immediately and comprehensively. In a healthy child the cardiovascular system has remarkable compensatory capability.

There is generally a stability of blood pressure and only an increase in heart rate and poor capillary refill time, until there is decompensation (with hypotension) which may lead to precipitous cardiac arrest.

In clinical edamination one must note following points very carefully, 5th point regarding the urine out put is an important point in history.

1. *Mental status:* Restlessness, agitation, anxiety, and progressive lethargy.
2. *Skin:* Temperature (hyperthermia or hypothermia), color, capillary refill time (normal <2 seconds), turgor, petechial rash may be present in meningococcemia or disseminated intravascular coagulation.
3. *Cardiovascular:* By far, the most significant physical finding in septic shock results from autonomic responses to stress. In children tachycardia occurs early. The younger the child, cardiac output is more dependent on heart rate rather than on increase in stroke volume.
   Alteration in blood pressure is a late manifestation of hypovolemia in children, occurring faster in children. Diastolic blood pressure begins to fall

Table 51.2: Organ dysfunction criteria

Cardiovascular dysfunction

- Despite administration of isotonic intravenous fluid bolus >40 ml/kg in 1 hour
- Decrease in BP (hypotension) <5th percentile for age or systolic BP >2 SD below normal for age (a)
  OR
- Need for vasoactive drug to maintain BP in normal range (dopamine > 5 mcg/kg/min or dobutamine, epinephrine, or norepinephrine at any dose
  OR
- Two of the following:
  - Unexplained metabolic acidosis: base deficit > 5.0 mEq/L
  - Increased arterial lactate >2 times upper limit of normal
  - Oliguria: urine output < 0.5 ml/kg/hr
  - Prolonged capillary refill: >5 sec
  - Core to peripheral temperature gap > 3°C

Respiratory dysfunction (b)

- $PaO_2/FIO_2 < 300$ in absence of cyanoptic heart disease or preexisting lung disease
  Or
- $PaCO_2 > 65$ torr or 20 mm Hg over baseline $PaCO_2$
  Or
- Proven need (c) or >50% FIO_2 to maintain saturation >92%
  Or
- Need for nonelective invasive or noninvasive mechanical ventilation (d)

Neurologic dysfunction

- Glasgow coma score < 11
  Or
- Acute change in mental status with a decrease in Glasgow coma score > 3 points form abnormal baseline

Hematologic dysfunction

- Platelet count < 80, 000/mm^3 or a decline of 50% in platelet count from highest value recorded over the past 3 days (for chronic hematology/oncology patients)
  Or
- International normalized ratio >2

Renal dysfunction

- Serum creatinine >2 times upper limit of normal for age or 2-fold increase in baseline creatinine.

Hepatic dysfunction

- Total bilirubin >4 mg/dL (not applicable for newborn)
  Or
- ALT 2 times upper limit of normal for age

{BP, blood pressure; ALT, alanine transaminase. (a) see Table 51.1; (b) acute respiratory distress syndrome must include a PaO_2/FiO_2 ratio < 200 mm Hg, bilateral infiltrates, acute onset, and no evidence of left heart failure. Acute lung injury is defined identically except the PaO_2/FiO_2 ratio must be <300 mm Hg; (c) proven need assumes oxygen requirements was tested by decreasing flow with subsequent increase in flow if required; (d) in postoperative patients, this requirements can be met if the patient has developed an acute inflammatory or infectious process in the lungs that prevents him or her from being extubated}

early as vascular tone begins to decrease. Systolic blood pressure is well maintained initially (normotensive shock) and only begins to fall once hemodynamic compromise is severe. Decreasing blood pressure signifies decompensated stage of shock (hypotensive shock). Hepatic enlargement and jugular venous distension with gallop rhythm may signify predominant cardiac involvement as part of septic myocardial depression or myocarditis. In warm phase of septic shock capillary refill time may be normal, however signs of hyperdynamic circulation, widened pulse pressure, hyperdynamic apex beat are important signs. Capillary refill time of more than 2 seconds is abnormal. Cold shock is more common than warm shock signified by peripheral extremity (hands and feet) temperature in neonatal and pediatric age group. It should be noted that warm shock with delay in treatment or if untreated will eventually result in cold shock.

4. *Respiratory:* Respiratory rate is increased to compensate for metabolic acidosis including lactic acidosis, secondly if ARDS is developing, progressive worsening of respiratory distress (tachypnea, nasal flaring, sternomastoid prominence, suprasternal, intercostal and subcostal retractions may occur with bilateral rales on auscultation or wheezes or unequal breath sounds depending upon presence of primary focus of infection in lungs.
5. *Urine output:* Oliguria is common possibly leading to anuria.

    It is also important to remember that physical finding will vary according to the stage of shock (compensated or decompensate). In severe cases patient may present with cardiopulmonary failure or cardiopulmonary arrest; both situations need aggressive hemodynamic support (fluids, inotropes and or vasopressors) as well as endotracheal intubation and mechanical ventilatory support for survival.

Emergency Management (Golden Hour of Sepsis Management)

The treatment of septic shock in children is aimed at optimizing perfusion of critical vascular beds and preventing or correcting metabolic abnormalities arising due to cellular hypoperfusion. The ultimate goals are to prevent or reverse the defects in cellular substrate delivery and metabolism and to support entire patient until homeostasis is restored.

For all forms of shock, treating the underlying cause is mandatory.

Speed is Essential

Delays in making the diagnosis and initiating treatment (fluid resuscitation as well as appropriate antibiotics), as well as suboptimal resuscitation, contribute to the developments of peripheral vascular failure and irreversible defects in oxygen use which can culminate vital organ dysfunction. The most effective and sensitive physicological monitoring available is, repeated and careful physical examination by an experienced and competent observer.

Management of child with septic shock is best started by aggressive goal directed management in the emergency department.

Priorities of Treatment

Two major priorities in treatment of septic shock in the golden hour are:

1. Rapid assessment of patient's disease process
2. Achievement of cardiopulmonary stability (Flow chart 51.1).

Approach or Management of Severe Sepsis or Septic Shock: (Time frames may overlap depending on hemodynamic status)

i. 0 min-5 min

Recognize decreased mental status and perfusion. Begin high flow oxygen. Establish IV/IO (Intravenous/intraosseous) access.

ii. 5 min to 40 min

Initial resuscitation: Push fluid boluses of 20 cc/kg isotonic saline or colloid up to and over 60 cc/kg (This could take 30 minutes or more. Use volumetric pumps or 60 ml syringe with three-way connector) until perfusion improves or unless rales or hepatomegaly develop. Correct hypoglycemia and hypocalcemia. Begin antibiotics (third generation cephalosporin and aminoglycoside). Recognize fluid refractory shock.

Simultaneously with 2nd peripheral IV start inotrope. Dopamine (even after second fluid bolus) at 10 µg/kg/min.

If hypotension with cold shock, start epinephrine early. (Use atropine/ketamine IV/IO/IM to obtain central access and airway at any time).

iii. 40 min to 60 min

Recognize fluid refractory dopamine resistant shock to 15 µg/kg/min.

Reverse cold shock by titrating central dopamine, or if resistant (normal or low blood pressure) titrate central epinephrine (0.05-0.3 microgram/kg/min).

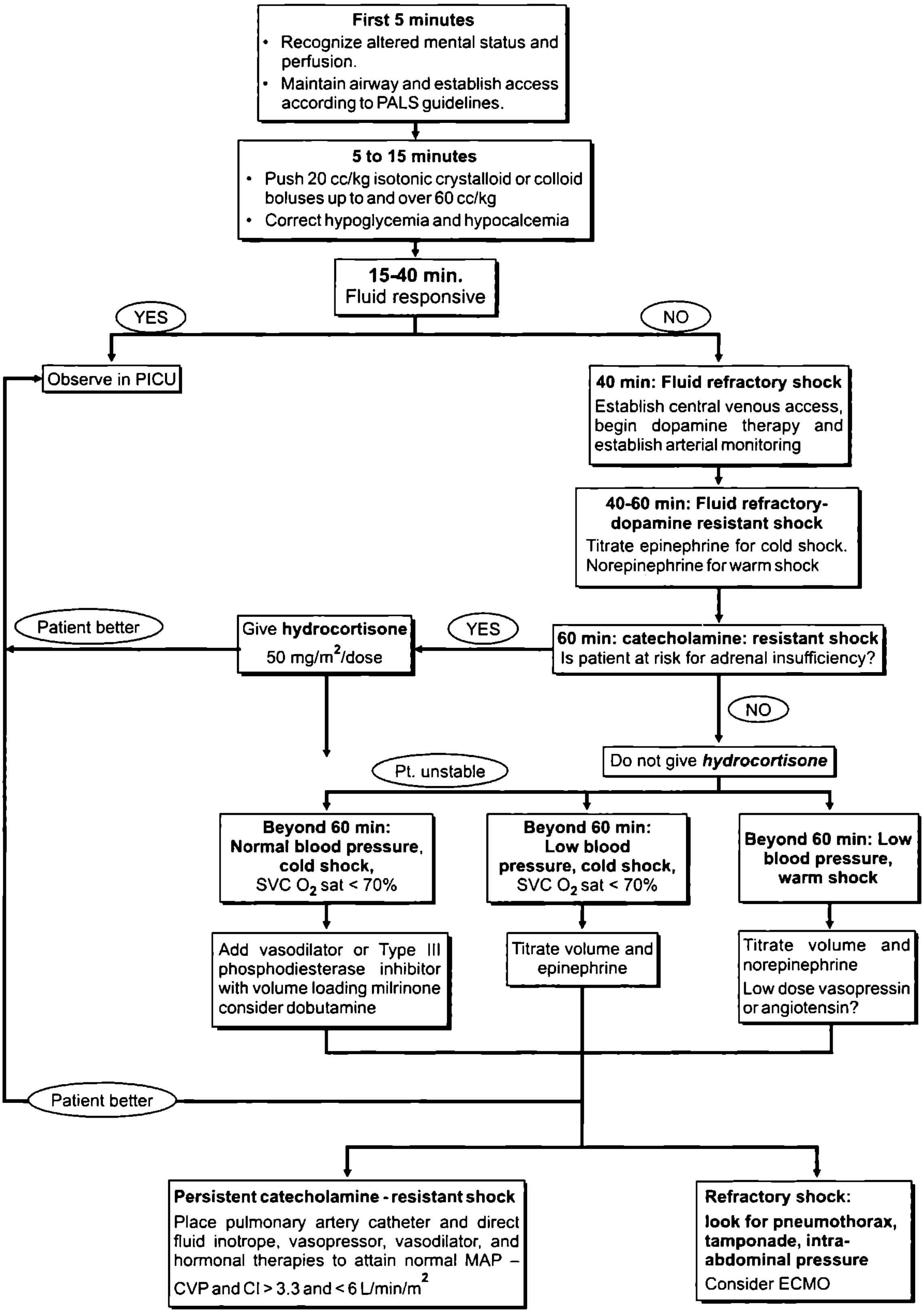
Reverse warm shock with low blood pressure by titrating central norepinephrine (Start at 0.1 µg/kg/min to titrate up to 1 µg/kg/min).
Shock not reversed?

iv. 60 min and beyond

Recognize catecholamine resistant shock.

Begin hydrocortisone (50 mg/m^2 dose) if at risk for absolute adrenal insufficiency.

Flow chart 51.1: Management of septic shock


First 5 minutes
• Recognize altered mental status and perfusion.
• Maintain airway and establish access according to PALS guidelines.
5 to 15 minutes
• Push 20 cc/kg isotonic crystalloid or colloid boluses up to and over 60 cc/kg
• Correct hypoglycemia and hypocalcemia
15-40 min.
Fluid responsive
YES
NO
Observe in PICU
40 min: Fluid refractory shock
Establish central venous access, begin dopamine therapy and establish arterial monitoring
40-60 min: Fluid refractory-dopamine resistant shock
Titrate epinephrine for cold shock. Norepinephrine for warm shock
Patient better
Give hydrocortisone 50 mg/m²/dose
YES
60 min: catecholamine: resistant shock
Is patient at risk for adrenal insufficiency?
NO
Do not give hydrocortisone
Pt. unstable
Beyond 60 min: Normal blood pressure, cold shock, SVC O₂ sat < 70%
Beyond 60 min: Low blood pressure, cold shock, SVC O₂ sat < 70%
Beyond 60 min: Low blood pressure, warm shock
Add vasodilator or Type III phosphodiesterase inhibitor with volume loading milrinone consider dobutamine
Titrate volume and epinephrine
Titrate volume and norepinephrine
Low dose vasopressin or angiotensin?
Patient better
Persistent catecholamine - resistant shock
Place pulmonary artery catheter and direct fluid inotrope, vasopressor, vasodilator, and hormonal therapies to attain normal MAP – CVP and CI > 3.3 and < 6 L/min/m²
Refractory shock:
look for pneumothorax, tamponade, intra-abdominal pressure
Consider ECMO

Consider use of vasodilator or phosphodiestrase inhibitor such as milrinone if cold shock and normal blood pressure (if available).

Consider vasopressin if warm shock with low blood pressure as a last resort.

Arrange transfer to PICU facility.

Once in PICU:

Monitor CVP, mean arterial pressure. Titrate fluids and inotropes to attain normal mixed venous oxygen saturation $ScVO_2 > 70$.

Depending on availability consider initiating further therpy as indicated: terlipressin, levosimendan, enoximone (not clearly established).

Relief of tamponade, such as pneumothorax, or pericardial tamponade, increased intraabdominal pressure due to fluid should be considered at any point.

DISCUSSION OF FLOW CHART 51.1

0-5 min

In the first five minutes initial assessment and management of child in shock includes recognition of decreased mental status, recognition of poor perfusion, administration of oxygen and establishment of intravenous access. High flow oxygen system, (e.g. Venturi masks) may be used.

All of the above are readily achievable in 1st five minutes.

However, if airway is unstable or the patient is lethargic or unresponsive and adequate oxygenation and ventilation is not achieved, endotracheal intubation and mechanical ventilation may be required. Implementation of this step may take additional time. Because mechanical ventilation abolishes or minimizes work of breathing, reduces oxygen consumption and improves oxygenation, early respiratory support benefits patients with severe shock in addition to those with ARDS/pulmonary edema.

Unfortunately no objective clinical criteria specific to pediatric septic shock for timing of endotracheal intubation (other than the standard indications, which include shock) exist in literature. Therefore, it is reasonable to consider endotracheal intubation when shock is persistant even after a volume resuscitation of >40-60 ml/kg. Children with sepsis requiring aggressive fluid resuscitation frequently have worsening tachypnea and increasing oxygen requirement clinically depicting early acute respiratory distress syndrome (ARDS) hand bagging 100 percent O_2 with PEEP valve may be best option waiting for PICU transfer. These patients will require early intubation and mechanical ventilation. The principles of lung-protective strategies (low tidal volumes and permissive hypercapnea) are applied to children as they are to adults. In premature infants, additional attention is paid to avoiding hyperoxemia to prevent retinopathy.

5-40 min

Initial Resuscitation

Preload and volume replacement: Fluid therapy by peripheral or intraosseous access should be initiated after adequate control of airway and breathing has been accomplished. Preload optimization is most efficient way of increasing cardiac output. Rapid intravascular volume expansion (as rapid as feasible) guided by repeated clinical examination and urine output is frequently adequate to restore blood pressure and peripheral perfusion.

Pulmonary edema with volume overload is rare in pediatric age group. Volume replacement of 20 ml/kg with isotonic solutions such as normal saline or Ringer's lactate can be safely given and repeated if necessary (typically 40-80 ml/kg is required) but up to 120-180 ml/kg fluid may be required in patients with bad capillary leak. Controversy continues about whether colloids or crystalloids are preferable.[11-13]

Choice of Fluid for Volume Replacement

Crystalloids

Crystalloids are readily available, cheap, convenient to use, free of side-effects. Crystalloids are rapidly distributed across intravascular and interstitial spaces. Volume 2-4 times of colloid is required for same volume expansion, and the effect may be transient due to leak in the interstitial space.

Albumin

Albumin should be used only in special circumstances, e.g. burns or documented hypoalbuminemia such as nephrotic syndrome. Recently one study in patients with malaria showed beneficial effect of albumin when compared to normal saline in fluid resuscitation.[11]

In resource limited countries cost of therapy is an issue while considering colloid solutions for expansion of plasma volume. In dengue shock syndrome three studies have looked at different fluid regimens with no significant differences[12-14] in outcomes.

Method of Fluid Administration

A 60 ml syringe filled with fluid drawn via the fluid bag with a three way connection can be conveniently used to push fluid boluses in the absence of a volumetric pump, in hypotensive patients.

Children normally have a lower blood pressure than adults and can prevent reduction in blood pressure by vasoconstriction and increasing heart rate. Therefore, blood pressure by itself is not a reliable endpoint for assessing the adequacy of resuscitation. However, once hypotension occurs, cardiovascular collapse may soon follow.

Hepatomegaly occurs in children who are fluid overloaded and can be a helpful sign of the adequacy of fluid resuscitation. Other practical ways to assess fluid overload are jugular venous distension, heart size rales and pulmonary congestion on chest X-ray. Bedside echocardiography should be used if available to assess cardiac function and signs of fluid overload. Gold standard to measure intravascular volume status still remains the measurement of a central venous pressure.

Hypocalcemia and Hypoglycemia

Before cardiac output and perfusion pressure are restored with drugs, electrolyte abnormalities (such as ionized hypocalcemia) that might impair cardiac performances should be corrected. Empirical calcium therapy may cause more harm than good by causing toxicity.

Hypoglycemia should also be corrected. Hyperglycemia should be avoided.

Insulin use for correcting hyperglycemia, has been advocated but no pediatric studies exist documenting improvement in outcomes.

Early Antibiotics

After appropriate cultures are taken, early use of broad spectrum systemic antimicrobial therapy based on clinical suspicious is reasonable although no randomized studies exist in children.[10] Commonly used antibiotics include a third generation cephalosporin such as ceftriaxone and an aminoglycoside such as amikacin. Adult data support use of early appropriate antibiotics to impact favorably on morbidity from septic shock.

Inotropic and Vasoactive Agents

Starting a second peripheral intravenous line and dopamine should be considered since fluid administration is ongoing.

40-60 min

Recognition of fluid refractory shock is important. If signs of shock persist despite adequate volume replacement and perfusion of vital organs is jeopardized. Inotropic drugs may be used to improve cardiac output.[15] The effects of particular drug in an individual patient are unpredictable and must be closely monitored. Ketamine and atropine should be used to obtain airway control and central line access. Various agents commonly used in pediatric ICU to increase myocardial contractility or to achieve peripheral vasoconstriction include:

Dopamine

It has alpha, beta and dopaminergic (delta) actions that are dose dependent.

At low doses (<3 mcg/kg/min) it primarily causes weak renal and splanchnic vasodilatation, and at 3 mcg to 10 mcg/kg/min it exerts a positive myocardial inotropic effect. At higher doses (>10 mcg/kg/min), it has strong vasoconstricting alpha effect, in addition to positive inotropic effect. So called 'renal dose' of dopamine (2-5 mcg/kg/min) for renal vasodilation has been over-emphasized and is of less practical significance in clinical setting. The primary indication for dopamine is the need to increase myocardial contractility after preload restoration. Usual dose is 5-20 mcg/kg/min titrated to desired effect. Dopamine (in doses >10 mcg/kg/min) should preferably, be given via central line to prevent ischemic necrosis of the skin.

Dobutamine

It is selective beta 1 agonist. It causes an increase in cardiac contractility and reduces peripheral resistance. The reduction in afterload and improved myocardial performance lowers ventricular filling pressures. Usual dose is 5 mcg to 20 mcg/kg/min. It should not be used alone in septic shock due to risk of further drop in blood pressure. In combination with dobutamine, any of the following dopamine, adrenaline, or noradrenaline can be used to prevent hypotension due to their vasoconstrictive action.

Adrenaline (Epinephrine)

It is an alpha and beta adrenergic agonist. It is used in situations where dominant hemodynamic feature is peripheral vascular failure as in septic shock. At higher doses severe vasoconstriction can lead to lactic acidosis and renal and splanchnic ischemia. The usual dose is 0.1 mcg/kg/min to 1 mcg/kg/min. It should be titrated closely and minimum dose should be used for required effect.

Noradrenaline (Norepinephrine)

An alpha and beta agonist (alpha >beta effect). Cardiac contractility is increased but it also causes massive increase in myocardial oxygen consumption and afterload, so cardiac output may not actually increase. Usual dose is 0.05-1 mcg/kg/min. In warm septic shock with hypotension despite use of adrenaline vascular resistance to improve blood pressure.

Beyond 60 min

Recognize Catecholamine Resistant Shock

Hydrocortisone therapy should be reserved for use in children with catecholamine resistance and suspected or proven adrenal insufficiency. Patient at risk include children with severe septic shock and purpura, children who have previously received steroid therapies for chronic illness, and children with pituitary or adrenal abnormalities. There is no clear consensus for the role of steroids or best dose of steroids in children with septic shock. Dose recommendations vary from 1 to 2 mg/kg for stress coverage (based on clinical diagnosis of adrenal insufficiency) to 50 mg/kg for empirical therapy of shock followed by the same dose as a 24 h infusion.[16-19] Current recommended dose is 50 mg/m^2 for 5 days.

At this point in time a decision to admit the patient to a PICU facility should have been made with further management guided by CVP monitoring, attaning normal mean arterial pressure and a mixed venous oxygen saturation >70 percent.

Further Management in PICU

Further titration of fluid and inotrope therapy will need invasive monitoring in the PICU. Attempt should be made to arrange transfer to a pediatric intensive care unit. In PICU the following therapies may be feasible, therefore these will be discussed in detail for the clinician who may have access to the latest technology and medications.

Cold shock with Normal Blood Pressure

Primary goal is to titrate epinephrine to achieve mixed venous oxygen saturations ($ScVO_2$) > 7 percent. Secondary goal is to titrate fluid therapy (volume loading) before adding a vasodilator such as nitrosovasodilator, milrinone or inamrinone (same as amrinone). Caution should be used in using afterload reduction indiscriminately in septic shock without simultaneous inotropic support. Both nitroprusside and nitroglycerin lower systemic vascular resistance in children and are usefu afterload reducing agents. These agents act via generation of nitric oxide. Nitroprusside has poten peripheral arterial vasodilating effects. Nitroglycerin is more potent venodilator and pulmonary vasodilator. Close monitoring and volume augmentation are frequently required when vasodilators are used to decrease pulmonary vascular resistance.

At alternative approach to improve cardiac contractility and lower systemic vascular resistance is based on the use of type III phosphodiesterase inhibitors (PDEI): milrinone and inamrinone.[20-25]

These are newer inotropic agents with properties of afterload reduction and myocardial diastolic relaxation (lusotropic effect). This class of agents, which includes milrinone and inamrinone [formerly amrinone, but the name was changed to avoid confusion with amiodarone], has a synergistic effect with beta-adrenergic agonists since the latter agents stimulate intracellular cAMP production while the PDE inhibitors increase intracellular cAMP by blocking its hydrolysis. Sinch the PDE inhibitors do not depend on a receptor mechanism, they maintain their action even when the beta-adrenergic receptors are down-regulated or have reduced functional responsiveness. The main limitation of these agents is their need for normal renal function (for milrinone clearance) and liver function (for inamrinone clearance). Inamrinone and milrinone are rarely used in adults with septic shock because catecholamine refractory low cardiac output and high vascular resistance is uncommon; however, this hemodynamic state represents a major proportion of children with fluid-refractory, dopamine-resistant shock. Fluid boluses are likely to be required if inamrinone or milrinone are administered with full loading doses. Because milrinone and inamrinone have long half-lives (1-10 hours depending on organ function) it can take 3 to 30 hours to reach 90 percent of steady state Milrinone is commonly used for cardiogenic shock which is frequently associated with septic shock.

Clinical Significance of Mixed Venous Oxygen Saturation ($ScVO_2$)

Because low CO is associated with increased O_2 extraction. $ScVO_2$ saturation can be used as an indirect indicator of whether CO is adequate to meet tissue metabolic demand.[26] If tissue oxygen delivery is adequate, then assuming a normal arterial oxygen saturation of 100 percent, mixed venous saturation is > 70 percent. Assuming a hemoglobin concentration of 10 gm/dl and 100 percent arterial O_2 saturation then a cardiac index (CI) > 3.3 L/min/m^2 with a normal oxygen consumption of 150 ml/min/m^2 (O_2 consumption = CI × (arterial O_2 content–venous O_2 content) results in a mixed venous saturation of > 70 percent because 150 ml/min/m^2 = 3.3 L/min/m^2 × [1.36 × 10 gm/dl + PaO_2 × 0.003] × 10 × [1-0.7]. In an emergency department study in adults with septic shock, maintenance of superior vena cava O_2 saturation >70 percent by use of blood transfusion to a hemoglobin of 10 gm/dl and inotropic support to increase cardiac output, resulted in a 40 percent reduction in mortality compared with a group in whom MAP and CVP were maintained at usual target values without attention to superior vena cava O_2 saturation.[27] Since 2002, Oliveria and colleagues reproduced this finding in children with septic shock reducing mortality from 39 to 12 percent when directing therapy to the goal of $ScvO_2$ saturation > 70 percent (personal communication).

Levosimendan[28-32]

Levosimendan is a promising new medication that increases Ca^{++}/actin/tropomyosin complex binding sensitivity and also has some Type III PDEI and ATP-sensitive K^+ channel activity. Because one of the pathogenic mechanisms of endotoxin induced heart dysfunction is desensitization of Ca^{++}/actin/tropomyosin complex binding, this drug allows treatment at this fundamental level of signal transduction overcoming the loss of contractility that characterizes septic shock. It does not increase the myocardial oxygen requirement.

Cold Shock with Low Blood Pressure

Epinephrine needs to be titrated to achieve $ScvO_2$ > 70 percent. If $ScvO_2$ is < 70 percent norepinephrine should be added. Dobutamine may be also need to be added. Milrinone may be considered as it is available in India. At the time of publication of these guidelines levosimendan and enoximone are not freely available in India.

Enoximone[33,34]

Enoximone is a Type III PDEI with 10 times more $beta_1$ cAMP hydrolysis inhibition than $beta_2$ cAMP hydrolysis inhibition. Hence it can be used to increase cardiac performance with less risk of undesired hypotension.

Warm Shock with Low Blood Pressure

In patients with warm shock with low blood pressure (septic vasodilatory shock), primary goal is to titrate norepinephrine to achieve mixed venous oxygen saturation above 70 percent indicating improved tissue oxygen delivery. Secondary goals include consideration of use of vasopressin if $ScVO_2$ continues to be less than 70 percent. Dobutamine and low dose epinephrine may be added.

Vasopressin (VP)

In severe warm shock with hypotension resistant to noradrenaline, vasopressin may be tried. Recent adult study showed no benefit NEJM 2008.[35] Terlipressin is also available. Vasopressin therapy should be considered in warm shock unresponsive to fluid and norepinephrine. Vasopressin does not use catecholamine receptors, and its efficacy is therefore not affected by ongoing alpha-adrenergic receptor down-regulation.

Action of VP are mediated via its three receptors subtypes designated as V1 (V1R/V1a), V2 (V2R) and V3 (V1b).[36]

V1 vascular receptors are loacted on vascular smooth muscle and mediate vasoconstriction. Additionally, V1 receptors are found in the kidney, myometrium, bladder, adipocytes, hepatocytes, platelets, spleen and testis. V1-receptors activation mediates vasoconstriction by receptor-coupled activation of phospholipase C and release of Ca^{++} from intracellular stores via the phosphoinositide cascase.[37]

V_2 renal receptors (V_2R), which cause the antidiuretic effects of vasopressin, are present in the renal collecting duct system and endothelial cells. Kidney V_2 receptors interact with adenylyl cyclase to increase intracellular cyclic adenosine monophosphate (cAMP) and cause retention of water.[37] V_3 pituitary receptors (formerly known as V1b) have central effects, such as increasing adrenocorticotropic hormone (ACTH) production, activating different G proteins, and increasing intracellular cAMP.[38]

VP also acts on oxytocin receptor which is important from the point of view of its vasodilator action on certain vital organs through nitric oxide (NO) mediated pathway. Blood flow within the coronaries, as well as the cerebral, pulmonary, and renal vascular beds, is preserved, promoting shunting to those areas. This regional vasodilation is likely the result of a complex interplay of vasopressin activity at V_1 and endothelial V_3 and oxytocin receptor sites producing an increase in nitric oxide release. In addition to these direct effects, vasopressin may also enhance or restore catecholamine sensitivity.

Synthetic vasopressin (8-arginine vasopressin) acts at the same receptor sites as endogenous vasopressin, producing an identical physiologic response.[38]

Terlipressin is a long acting analogue of vasopressin that has been shown to have higher affinity for vascular receptors than vasopressin and has demonstrated potent vasopressor effects in adult patients with norepinephrine resistant septic shock.[39]

Although angiotensin can also be used to increase blood pressure in patients who are refractory to norepinephrine, its clinical role is not as well defined.[40]

Phenylephrine is an another pure vasopressor with no beta adrenergic activity.[41] Its clinical role is also limited. Vasopressors can be titrated to end points of perfusion pressure (MAP-CVP) or systemic vascular resistance that promote optimum urine output and creatinine clearance,[42-44] but excessive vasoconstriction compromising microcirculatory flow should be avoided.

Low dose arginine vasopressin (AVP; in doses $\leq$ 0.04 units/kg/min) as an adjunctive agent has short-term hemodynamic benefits in adults with vasodilatory shock. It is not currently recommended for treatment of cardiogenic shock, hence it should not be used without $ScVO_2$/cardiac output monitoring. Because vasopressin is destroyed by gastric trypsin, it must be administered parenterally.

Vasopressin is reapidly degraded by enzymes in the liver and kidneys, with elimination half-life of approximately 10 to 35 minutes.[35] Renal insufficiency and hepatic failure prolong its half-life.

Dosing, Preparation and Administration

Vasopressin is available as a 20 units/ml injection. For continuous intravenous infusion, it should be diluted with normal saline or 5 percent dextrose to a final concentration of 0.1 to 1 unit/ml. Administration through central venous accesss is recommended to minimize the risk of extravasation. Although the stability of vasopressin infusions with other drugs has not been studied, a recent report on bolus vasopressin administration found it to be compatible with most of the drugs used commonly in the ICU.

Studies of vasopressin in adults with vasodilatory shock have used infusion rates of 0.01 to 0.1 units/min. In pediatrics patients, a vasopressin dose of 0.3 to 2 milliunits/kg/min (equivalent to 0.0003 to 0.002 units/kg/min or 0.01 to 0.12 units/kg/hr) is recommended, based on the report by Rosenzweig.[45] The infusion should be titrated to optimized blood pressure and perfusion. It has been suggested that vasopressin infusion may be tapered over a 2 to 3 hours period, once blood pressure and the doses of concomitant catecholamine infusions are stabilized.

Though, vasopressin has been shown to increase mean arterial pressure, systemic vascular resistance, and urine output in patients with vasodilatory septic shock and hyporesponsiveness to catecholamines effect on outcomes is not established.[45-50]

Terlipressin has been reported to reverse vasodilated shock in several pediatric studies.[51-54] The only significant difference between vasopressin and terlipressin is that terlipressin is a long acting form of vasopressin acting on same receptors.

In conclusion, the effect of low dose AVP on clinically important outcomes. Such as mortality remains uncertain.

In case of persistent catecholamine resistant shock at any point of time, one must rule out mechanical causes of shock such as tamponade due to pericardial effusion, pneumothorax or increased intra-abdominal pressure (example, patients with severe ascites in leaky pahse of dengue shock syndrome). Beyond 60 minutes refractory shock has a high mortality, specially since measure described such as extracorporeal membrane oxygenation (ECMO) and continuous renal replacement therapy (CRRT) are not readily available.

THERAPEUTIC END-POINTS

1. Therapeutic end-points following above mentioned interventions are capillary refill of <2 sec, normal pulses with no differential between peripheral and central pulses, warm limbs, urine output of > 1 ml/kg/hr, normal mental status, decreased lactate, and increased base deficit and superior vena cava or mixed venous oxygen saturation of > 70 percent.
2. When employing measurements to assist in identifying acceptable cardiac output in children with systemic arterial hypoxemia such as cyanotic congenital heart disease or severe pulmonary disease, arterial-venous oxygen content difference is a better marker than mixed venous hemoglobin saturation of oxygen.
3. Optimizing preload optimizes cardiac index. As noted above, blood pressure by itself is not a reliable end point for resuscitation.

CONCLUSIONS

Sepsis is a common problem with high mortality in neonates and children but in past decade mortality has significantly decreased in developed world however it is still high in the developing world.

Infants and children are recongnized to have more difficult intravenous access, therefore necessitating use of intraosseous access as required. Early fluid resuscitation (crystalloid or colloids) based on weight with 40-60 ml kg or higher may be needed. Central line is difficult to insert, therefore use of peripheral dopamine has been included in guidelines.

Decreased cardiac output and increased systemic vascular resistance tends to be most common hemodynamic profile. Dopamine is recommended as the initial agent for hemodynamic support. Epinephrine is recommended for cold shock, on non-epinephrine for warm shock. Milrinone and dobutamine are recommended for poor myocardial contractility with normal blood pressure. Early appropriate antibiotics, correction of hypoglycemia, hypocalcemia and avoiding hyperglycemia are recommended. Pediatric recommendations include use of rapid cardiopulmonary assessment and greater use of physical examination for achieving therapeutic end-points. CVP monitoring should be attempted whenever possible. Early mechanical ventilation should be considered if hemodynamic instability continues beyond fluid therapy.

Issue of steroids for therapy of septic shock remains unsettled, although recommendation includes use of steroids for catecholamine unresponsive shock in presence of a suspected or proven adrenal insufficiency. Role of vasopressin or terlipressin on outcomes is unclear however, may be considred in nor epiresistant vasodilatory shock. Further fluid therapy and inotropic support can be guided by CVP once a PICU facility is available,[55] and mixed venous oxygen saturations can be monitored.

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CHAPTER

Multiorgan Failure in Critically Ill Children

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Physicians involved in care of critically ill children in multidisciplinary pediatric intensive care units are increasingly becoming aware of an entity called multiple organ dysfunction syndrome (MODS). As supportive care given to these critically ill patients is getting better, one is seeing longer survival and subsequent multiorgan complications. Focus has shifted from one organ support to multiorgan support of these patients as frequently these children die of multiorgan dysfunction and not the primary disease they were admitted with.

Definition

The multiple organ dysfunction syndrome (MODS) has been characterized as loss of normal functioning of more than two vital organ systems the cardiovascular system, the lung, liver, kidney and hematological system following a wide variety of injuries (see chapter on Pediatric Septic Shock: Table 51.2).

Sequential multiple organ failure (MOF) has become a recognized disease entity occurring in response to infection, perfusion deficits, a persistent inflammatory focus, or a persistent focus of dead and/or injured tissue. At least four phases can be identified in what is usually a 21 to 28-day ICU course.

Historical Perspective

Single organ failure has long been recognized as a cause of morbidity and mortality in hospitalized patients. In trauma centers in the late 1960s, a new form of organ failure was recognized—sequential failure of lung, liver, and kidney, usually followed by death.[1]

By the mid-1970s, the syndrome was observed after other etiologies such as ruptured abdominal aortic aneurysms and infection. The syndrome of MODS post-injury is now recognized as a pathological process whose outcome depends in part on the etiology. MODS occurs in only a small fraction of polytrauma patients but remains the main cause of late mortality in adult patients after trauma.[2] Progressive MODS in adults continues to carry a high mortality risk, approaching 75 to 90 percent after septic shock.[3] The acute respiratory distress syndrome (ARDS) occurs after a variety of etiologies, and forms a crucial component of MODS, carrying a mortality risk of 40 to 60 percent. It has been recognized increasingly that death in critically ill adult patients results frequently from the systemic derangements accompanying MODS.[4-5]

In the mid-1980s, reports demonstrated the occurrence of organ system dysfunction in a large cohort of children admitted to a tertiary pediatric ICU. In a further series, the same authors reported on mortality when sepsis was associated with MODS. In 1994 Proulx reported on the timing and predictors of MODS in a series of 777 consecutive patients younger than 18 years of age. In that study, the overall mortality rate was 50 percent, with 88 percent of all mortality occurring within 7 days of admission to the PICU.[6] The most recent series detailing the epidemiology of MODS in 1058 children demonstrates patterns of injury and incidence of MODS similar to earlier reports. The initial reports indicated an overall incidence of MODS, i.e. 2 organ system dysfunctions, in children admitted to tertiary care PICUs at 27 percent.[7]

The mortality for pediatric patients depended on the number of organ systems that met the definition of dysfunction and were 1 percent, 11 percent, 50 percent, 75 percent for one, two, three and four dysfunctional organ systems, respectively with an overall mortality of 54 percent for patients with two or more dysfunctional organ systems compared with 0.3 percent for children without MODS.[8]

Of note in the reports of pediatric MODS was the different pattern of organ system involvement when compared with adults.[9-14]

Clinical Epidemiology

MODS evolves over several phases, the biology of which changes over time. These phases are shock, resuscitation, postresuscitative hypermetabolism or persistent inflammation, and the clinical MODS (Table 52.1). In the initial shock and resuscitation phases, the biological derangements frequently involve abnormalities of perfusion and oxygen transport with the endothelial cell playing a central role. In the hypermetabolism organ failure phase, the biological response appears dominated by mechanisms of metabolic dysregulation with activated phagocytes. With continuation of the hypermetabolic phase and failure to resolve the inflammatory stimuli, the clinical phase of MODS is entered. Timely recognition and intervention in each phase is crucial to reducing the mortality associated with progressive MODS.

Most pediatric and adult patients make a successful and complete recovery after (1) resuscitation from shock, (2) control of the inciting source, and (3) provision of supportive measures. In a subset of patients, a phase of persistent hypermetabolism is entered. Once activated, even with control of the inciting source, this hypermetabolic phase can persist for 10 to 21 days. In patients who recover, the hypermetabolism spontaneously abates; however, the mortality risk in this phase of persistent hypermetabolism appears to be in the 25 to 40 percent range.[15]

The events that most commonly set the stage for the development of hypermetabolism are similar to the common etiologies of all shock states treated in the ICU and emergency room. These events fall into a circumscribed set of clinical scenarios and include severe hemorrhage, sepsis of any etiology, ischemia, mechanical or thermal tissue injury, or severe inflammation as may be seen in pancreatitis or immune dysregulation, e.g., erythrohemophagocytic syndrome. These events are usually preceded by an absolute or relative perfusion deficit, i.e. distributional shock, that may or may not be associated with the usual clinical signs of circulatory insufficiency, such as hypotension or oliguria. Rapidity and adequacy of the resuscitation appear to be major determinants of whether the patient progresses to hypermetabolism and ultimately MODS.

Clinical features of the hypermetabolic phase include fever, leukocytosis, tachycardia, oliguria, tachypnea, encephalopathy and coagulopathy. The development of lung infiltrates on chest X-ray and progressive worsening of the alveolararterial oxygen gradient characterize the respiratory failure, that is an integral feature of the syndrome.

Characterization of MODS takes one of two forms relative to the initiating event.[16] In the first variation, frequently seen after a primary pulmonary initiating event such as aspiration, MODS is a terminal event, becoming manifest only a few days

Table 52.1: Stages of multiorgan dysfunction syndrome (MODS)

Clinical stage	*Physiology*	*Therapy*
Shock	Defective substrate delivery	Re-establish circulation and pulmonary gas exchange
Resuscitation	Microcirculatory dysfunction	Optimize O_2 delivery and metabolite clearance in periphery
Hypermetabolism	MODS	Dysregulation of metabolism, Support of organ system function, Modulation of inflammation and immune function, Optimize tissue repair

before death. In the second, more common form of MODS, seen after septic or hypovolemic shock with ARDS, MODS is present nearly from the time of injury but does not become progressive until 7 to 14 days after injury. The onset of progressive MODS is heralded by the onset of progressive jaundice and hyperbilirubinemia, usually by 6 to 10 days postinjury, and the onset of progressive renal failure with a rising serum creatinine, usually 10 to 14 days postinjury. While insufficient data exist to formally define such patterns of injury in critically ill children, close observation of organ system function is important in detecting early deterioration in function before the onset of irreversible changes. Recommended studies for such surveillance include coagulation function, liver enzymes, bilirubin, plasma ammonia, creatinine, blood urea nitrogen (BUN), and alveolararterial oxygen gradient. Deviations from normal values or progressive deterioration in function heralds the possibility of impending organ system failure.

Several clinical settings are associated with the transition from hypermetabolism to organ failure. These include a persistent or unrecognized perfusion deficit, a persistent focus of infection, recurrent bacteremias as might be seen with colonization of indwelling devices, or a persistent inflammatory focus in the absence of infection. The terminal phase of MODS is frequently associated with profound hepatic insufficiency. The transition to clinical MODS is a significant prognostic event because it heralds a change in mortality risk from 25 to 40 percent range to 40 to 60 percent range in the early stage and to 90 to 100 percent range in the late stage of MODS.

Pathogenesis

Organ injury does not directly result from exogenous factors such as bacteria or bacterial toxins but is to a great degree a result of the body's production of immunoinflammatory factors. The concept of activator-mediator-responder is useful in conceptualizing the pathogenesis of hypermetabolism-MODS. Dead or injured tissue, invasive organisms, and shock are currently recognized activators. These systems interact with each other providing amplification of the host response.

Systemic Inflammatory Response Syndrome (SIRS)

Most inciting events start with a local injury from trauma, infection, or lack of perfusion. A local inflammatory response occurs, presumably from the products of platelet activation, endothelial injury, and tissue factor release with activation of complement, coagulation, and the kallikrenin system. The local mediator rich milieu that develops can then initiate a distant systemic response, particularly after resuscitation of these injured beds has occurred and flow has been reestablished. Local and systemic responses can also be induced by direct action of the microbial toxins or components of the microorganism. The gut has been a major focus of recent research into the pathogenesis of MODS. The intestinal mucosa is particularly susceptible to ischemia/reperfusion injury. Loss of gut barrier function leading to so-called luminal bacteria has been noted after shock in a wide variety of settings.[17]

The liver plays a crucial role in filtering out blood derived from the entire gastrointestinal (GI) tract. Through its biochemical regulatory function, it controls blood protein and chemistry. In addition, it detoxifies the portal blood by removing viable bacteria and endotoxin, as well as other toxic substances produced through the luminal degradation of nutrients, e.g. ammonia.

Several pieces of evidence implicate a critical relationship between compromised hepatic function and acute lung injury, the mortality for patients with advanced cirrhosis, who develop ARDS, is greater than would be predicted in the absence of the hepatic disease and, secondly, ARDS that develops during acute hepatic allograft rejection reverses rapidly after retransplantation.

In patients admitted after trauma or surgical procedures, the wound plays a central role in the initiation and maintenance of the systemic response.

The transition from hypermetabolism to MODS is a significant clinical and prognostic event and probably signals the overt manifestation of irreversible cell injury.

Systemic Physiology

The movement of oxygen, the regulation of its distribution between and within tissues, and the monitoring of cellular metabolism are all important in the clinical management of critically ill patients. Patients with sepsis or *the systemic inflammatory response syndrome* have a hemodynamic disturbance characterized by a raised cardiac output and reduced systemic vascular resistance. Although delivery of oxygen may be maintained or even increased by pharmacological means, most patients have poor peripheral uptake of oxygen.

The cause of this phenomenon remains unclear. However, sepsis and systemic inflammatory response syndrome are associated with damage to the vascular endothelium, which normally produces vasoactive substances that regulate microvascular blood flow to ensure that all organs are adequately oxygenated. The microcirculation may, therefore, be disrupted. In addition, inflammatory mediators may directly modulate the intracellular mechanisms that regulate use of oxygen, including mitochondrial function. These two factors mean that patients with sepsis or the systemic inflammatory response syndrome commonly develop multiple organ failure, to which many succumb. Nevertheless, not all patients at risk of developing sepsis and multiple organ failure do so, and individual susceptibility varies widely. The clinical result of this disturbance is tissue hypoxia.

Detection of Tissue Hypoxia

The clinical signs of tissue hypoxia are largely nonspecific. However, increased respiratory rate, peripheries that are either warm and vasodilated or cold and vasoconstricted, poor urine output, and mental dullness may indicate organ dysfunction and should prompt a search for reversible causes. The following biochemical and physiological measurements may be helpful.

Metabolic Acidosis

A low arterial pH and high blood lactate concentration may be important. Anaerobic production of lactate may occur secondary to global hypoxia or focal hypoxia or through nonhypoxic causes. A wide arterialmixed venous carbon dioxide pressure gradient (1 kPa) has been shown to be relatively insensitive as a marker of anaerobic tissue metabolism.

Oxygen Extraction Ratio

The uptake of oxygen by tissues (VO_2) is normally independent of oxygen delivery (DO_2). If delivery fails, the oxygen extraction ratio (VO_2/DO_2) rises to maintain a constant rate of uptake and fulfill tissue demand. The compensatory mechanisms fail only at very low oxygen delivery levels (termed critical DO_2), when extraction starts to fall and becomes dependent on delivery. However, patients with sepsis or the systemic inflammatory response syndrome have a low oxygen extraction ratio, indicating poor tissue uptake or use. Changes in oxygen delivery and uptake relations have been used to identify occult tissue hypoxia and predict outcome since those who survive septic shock tend to achieve normal oxygen extraction levels.[18-22]

A high mixed venous oxygen saturation, measured through a pulmonary artery catheter, indirectly indicates a low oxygen extraction ratio.

Gastric Mucosal pH (pH1)

Gastric mucosal pH can be measured using a tonometer, originally a saline filled balloon placed in the gastric lumen. Several studies have found that a falling or persistently low gastric mucosal pH is associated with poor prognosis in critically ill patients. However, whether gastric mucosal pH truly provides evidence of gastric mucosal hypoxia, remains uncertain.

Injury to Individual Organs

Lung Injury

About 35 percent of patients with sepsis develop mild to moderate acute lung injury and a quarter have fully developed acute respiratory distress syndrome. Affected patients have increased pulmonary vascular permeability, which leads to alveolar edema and refractory hypoxemia. Lung injury rarely occurs in isolation. It is usually the pulmonary manifestation of a pan-endothelial insult with inflammatory vascular dysfunction.

Acute lung injury and the acute respiratory distress syndrome may have different causes as the acute respiratory distress syndrome is partly determined by the nature of the underlying or precipitating condition. Moreover, the precipitating condition and coexisting multiple organ failure dictate outcome.

Cardiovascular Injury

Myocardial dysfunction also complicates sepsis and the systemic inflammatory response syndrome. Ventricular dilatation occurs in patients with septic shock, and the ejection fraction may be reduced to around 30 percent despite an overall rise in measured cardiac output. Patients who die tend to have had lower-end diastolic volumes and less compliant ventricles during diastole than survivors.

Systemic vascular resistance is also low in sepsis, possibly through over expression of vasodilator substances such as nitric oxide and cyclooxygenase products in the vascular smooth muscle. The consequent loss of vasoregulation may result in poor distribution of perfusion and tissue hypoxia.

Optimization of left ventricular filling pressure, inotropic support, and vasoconstrictors such as noradrenaline are all beneficial in septic shock. In addition, novel pressor agents, such as nitric oxide synthase inhibitors have been advocated recently for patients with refractory septic shock.

Renal Failure

Acute renal failure is a common complication of sepsis and the systemic inflammatory response syndrome. This may reflect changes in the distribution of intrarenal blood flow between the cortex and medulla. The ability of patients to maintain intravascular homoeostasis may also be impaired. The early use of hemofiltration to correct fluid imbalance and (possibly) remove circulating inflammatory mediators has been advocated, but the benefits are unproven. It is essential to restore circulating volume and achieve an adequate blood pressure and cardiac output to prevent and treat acute renal failure.

Dysfunction of Gastrointestinal Tract

The bowel is particularly susceptible to ischemic insults. Hypoperfusion of the gastrointestinal tract is thought to be important in the pathogenesis of multiple organ failure as outlined above. Hepatic dysfunction, possibly resulting from reduced blood flow relative to metabolic demand, is also common in critically ill patients. Maintaining adequate flow and perfusion pressure are the only proved treatments to correct these deficiencies. Inotropic drugs with dilator properties such as dopexamine may selectively enhance splanchnic perfusion and oxygenation.

Current Therapy: Multiorgan Support is the Key

Current therapy of MODS is aimed at prevention and supportive care. Three general areas are—*source control, restoration and maintenance of oxygen transport and metabolic support.*[23]

Source control is a major emphasis, as persistence of a source guarantees a high mortality risk from MODS. Whenever possible, excision or removal of the inciting cause is desirable. Appropriate antimicrobial agents are important when the septic focus cannot be removed.

Flow dependent oxygen consumption is treated with the comprehensive approach. Oxygen content is increased by providing an arterial oxygen tension that maintains hemoglobin saturation > 90 percent and ensuring a hemoglobin > 9 gm range. Malnutrition is one of the primary manifestations of MODS. Nutritional support *per se* does not alter the course of the disease process but can effectively control the visceral malnutrition and limit the lean body mask.

To achieve these ends effectively, following principles should be applied:

1. Avoid excess total calories and excess glucose by providing 45 to 55 total Kcal/kg/day in children > 10 kg body weight or 55 to 75 Kcal/kg/day in children weighing < 10 kg, with approximately 6 to 8 mg/kg/min in older children.
2. Restrict current fat emulsions to 1 to 2 gm/kg/day to avoid fat overload syndrome.
3. Achieve nitrogen equilibrium by titrating the dose of amino acids. Modified amino acids are a more efficient protein source than standard amino acids formulas.
4. Provide the necessary vitamins, minerals, trace elements and micronutrients.
5 Enteral feeding with easily observed formulas appropriate for age to minimize loss of gut mass and integrity.

With above principles in mind the overall mortality, the incidents of MODS and the mortality of MODS are significantly reduced. The incidence and mortality risk of ARDS, however, seems to be unchanged.

Newer Therapies

Newer therapies are being developed based on the biology of the syndrome. The approach to these therapies considers systemic inflammation to be the pathogenetic mechanism, with MODS resulting from persistent or excessive inflammation. The therapies being developed are designed to suppress elements of inflammation and to promote reparative processes.

Clinical trials with single agent chemotherapy, such as insulin, steroids, growth hormone, PGE, and enteral nutrition have shown no significant improvement in the occurrence of or survival from MODS. Experimental studies with other single agent chemotherapies are producing conflicting results; however, it appears as there is no "magic bullet" yet. In adult trials activated protein C infusion (24 microgram/kg/hr for 96 hours) modulate sepsis cascade. It has been shown to decrease mortality in severe sepsis. Protein C is not indicated in children.

One study performed in adult patients with severe sepsis and multiorgan (two or more organs) failure: Reduction in mortality by 7.4 percent.[24]

It is relatively contraindicated if patient has any of the following:

Internal bleeding, low platelet count (below 30000 per cumm), on heparin therapy, chronic severe liver disease, and increased ICP.

There are few reports on use of activated protein C (Xigris infusion) for pediatric patients with meningococcemia with promising results in dosage of 24 microgram/kg hour for 96 hours.[25-27]

Obviously, large multicenter trials are needed to establish the role of activated protein C in pediatric septic shock.

CONCLUSIONS

- Organ dysfunction probably arises from abnormalities of microvascular control and cellular metabolism.
- Susceptibility to the effects of inflammatory activation may be determined genetically.
- The gastrointestinal tract seems to be the "motor" of sepsis.
- New supportive and therapeutic interventions are emerging as understanding of sepsis increases.
- The best treatment remains prevention. Once initiated, the practice of sound critical care principles in a setting of source control provides the most optimal chance of survival.
- Mortality is directly related to numbers of organs involved.

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CHAPTER

Viral Hemorrhagic Fever: Management in Pediatric Intensive Care Unit

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A small number of viruses have established notoriety by virtue of their capacity to cause clinical syndromes with hemorrhagic manifestations. About 12 distinct viruses causing hemorrhagic fever, all with enveloped RNA, are members of four viral families[1] (Table 53.1). A recent example of these viral hemorrhagic fevers (VHF) was an outbreak of dengue in 1996, and was associated with significant mortality in India.[2] Recently, in year 2001 increasing number of cases of dengue or other viral hemorrhagic fevers are being referred to and getting treated at our institution and elsewhere. These agents produce

Table 53.1: Epidemiological features of viruses causing viral hemorrhagic fevers

Family of virus	*Disease*	*Endemic areas*	*Modes of transmission*	*Incubation period (days)*	*Ribavirin useful*	*Vaccine*
Flaviviridae						
Yellow fever	Yellow fever	Sub-Saharan Africa, tropical America	Mosquito borne	3-5	No	Yes
Dengue	Dengue fever, dengue hemorrhagic fever, dengue shock syndrome	Asia, Africa, Pacific America	Mosquito borne	3-14	No	
Kyasanur forest	Kyasanur forest disease	Southwest India	Tick borne	3-8	No	Yes
Omsk	Omsk hemorrhagic fever	Russia	Tick borne, muskrathuman	3-8	No	Yes
Arenaviridae						
Lassa	Lassa fever	West Africa	Rodent-human	6-21	Yes	No*
Junin	Argentinian hemorrhagic fever	Argentina	Rodent-human	7-16	Possibly	Yes
Machupo	Bolivian hemorrhagic fever	Bolivia	Rodent-human	7-16	Possibly	No
Gunarito	Venezulian hemorrhagic fever	Venezuela	Rodent-human	7-16	No	No
Sabia	Brazilian hemorrhagic fever	Brazil	Rodent-human	7-16	No	No
Banyaviridae						
Phlebovirus	Rift valley fever	Sub-Saharan Africa	Mosquito borne	3-12	?	No**
Nairovirus	Crimean-congo hemorrhagic fever	Africa, Asia, Middle East	Tick borne, Nosocomial	3-12	Possibly	Yes
Hantaviruses	Hemorrhagic fevers with renal syndromes	Asia, Europe, Eurasia	Rodent-human	days 2-weeks	Possibly	No*
Filoviridae						
Ebola	Ebola hemorrhagic fever	Africa	person-person	2-21	No	No
Marbung	Marbung virus disease	Sub-Saharan Africa	Person-person	3-9	No	No

* In development.

** Live attenuated vaccine available for domestic livestock; human vaccine experimental a wide spectrum of disease severity, but the most extreme manifestations include circulatory instability, increased vascular permeability, diffuse hemorrhages and in some cases rapidly progressing acute respiratory distress syndrome (ARDS) and multiorgan failure. In this chapter clinical management issues in treating VHF presenting as critical illness, admitted to pediatric intensive care unit with special reference to increased severity of clinical presentation such as shock, severe bleeding manifestations, disseminated intravascular coagulation and multiorgan failure will be discussed.

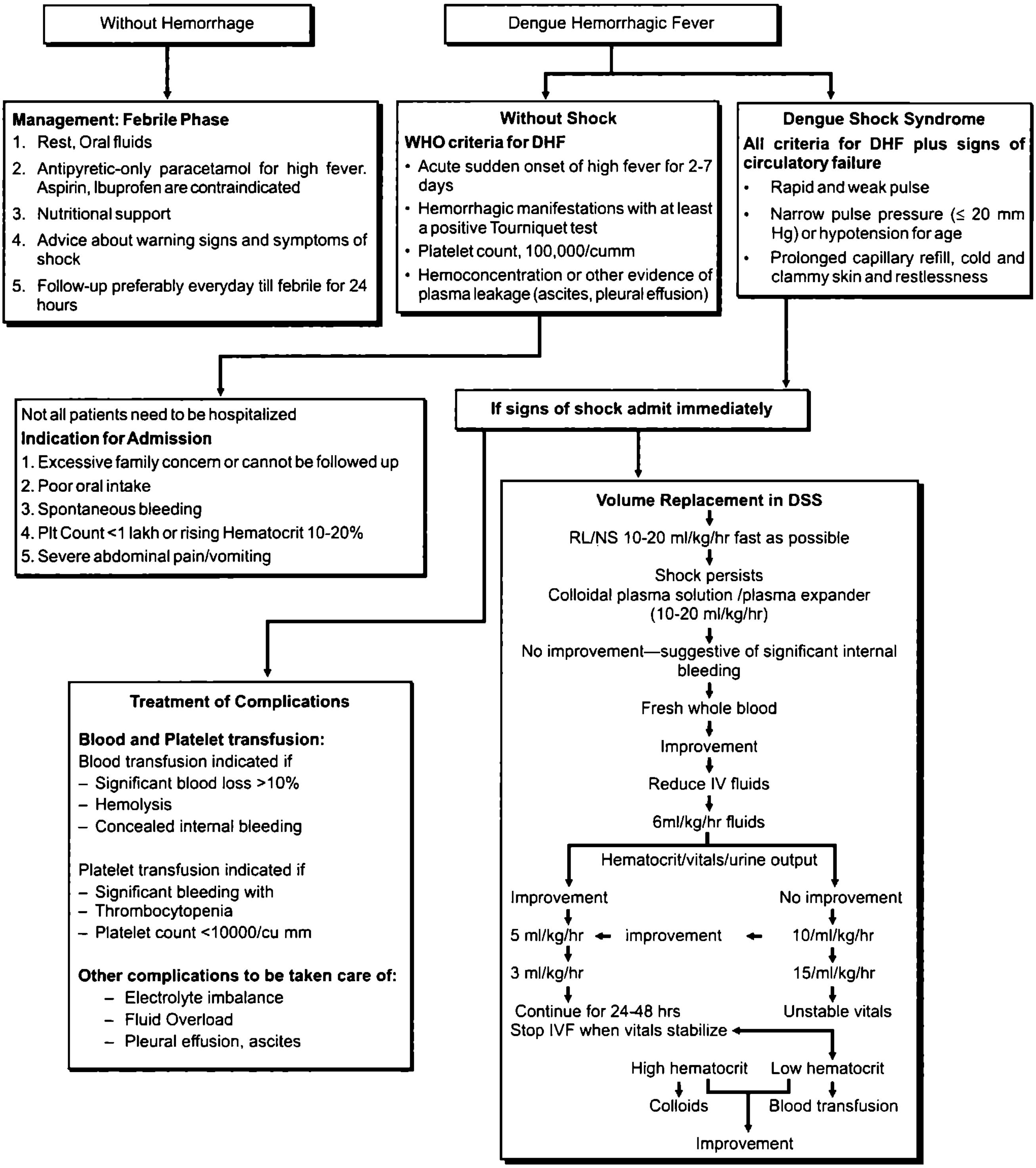
Etiopathogenesis

Most accepted hypothesis explaining pathogenesis of these fevers is immune enhancement hypothesis.[3] Upon entry of virus into human body by mosquito (*Aedes Egypti*) bite, rapid viral replication occurs within monocytes and macrophages by antibody dependant enhancement, releasing various vasoactive mediators such as tumor necrosis factor, interleukins, platelet and complement activating factors, gamma interferons resulting in increased vascular permeability.[3,4] A recent study also suggested imbalance between thromboxane A2. (TXA2) and prostaglandin I_2 (PGI2) production in dengue hemorrhagic fever (Flow chart 53.1). Progressive reduction of plasma TXA2/PGI2 ratio leads to further overt and serious manifestations.[5] Capillary damage allows fluid, electrolytes, proteins and in some instances, red blood cells to leak into intravascular spaces. This internal redistribution of fluid together with deficits due to gastrointestinal fluid losses due to vomiting results in hemoconcentration, hypovolemia, increased cardiac work, tissue hypoxia, metabolic acidosis hyponatremia and multiorgan failure.[6] Severe Thrombocytopenia, disseminated intravascular coagulation with liver involvement, contributes additively to produce hemorrhagic manifestations.

Clinical Features

These fevers usually share common clinical manifestations which in addition to bleeding phenomenon include sudden onset, prominent constitutional symptoms, fever that may be biphasic, relative bradycardia, characteristic hematologic abnormalities, of leukopenia, hemoconcentration, occasionally disseminated intravascular coagulation.[7] Dengue is the most common VHF in our country. Biphasic fever and rash are the most characteristic features of the dengue fever syndrome. In classic dengue fever, after an incubation period of 2 to 7 days, there is a sudden onset of fever, which rapidly rises, usually accompanied by frontal or retro orbital headache. Occasionally back pain precedes the fever. A transient macular, generalized rash that blanches on pressure may be seen. Myalgia, bone pain, nausea, vomiting, and anorexia may develop. Coincident with one or two days after defervescence, a generalized, morbilliform, maculopapular rash appears, sparing palms and soles. It disappears within 1-5 days. About the time of appearance of this second rash, the body temperature, which has fallen to normal, may become elevated slightly and establish the biphasic temperature curve. Clinical picture of encephalopathy can be present in some cases.[8,9] *A strong indication to admit to pediatric intensive care unit* includes tachycardia, cold extremities, poor capillary refill, decreased systolic and diastolic pressure with decreased pulse pressure indicating rapid progression to dengue shock syndrome (DSS). If aggressive mangement of shock is not undertaken at this point, progressive metabolic acidosis will lead to irreversible shock, associated with multiorgan failure and poor outcome. In addition to manifestations of shock, respiratory distress (grunting, tachypnea, nasal flaring, suprasternal, intercostals and subcostal retractions) with increasing oxygen requirement in a patient admitted to ward indicates increasing capillary leakage with progressive pleural effusion and ascietis necessitating admission to pediatric intensive care unit. Deteriorating mental status should also be considered as an indication to admit to pediatric intensive care unit. Infants and young children can present with shock, encephalopathy, seizures and massive intracranial bleeding with raised intracranial tension as well as manifestations of acute respiratory distress syndrome with massive right sided pleural effusions and ascietis further contributing to respiratory distress. World Health Organization (WHO) has graded dengue fever into four grades as per severity of illness[10] (Table 53.2). Grade III and grade IV patients (DSS) require admission to pediatric intensive care unit.

Flow chart 53.1: Dengue fever



Management: Febrile Phase

1. Rest, Oral fluids
2. Antipyretic-only paracetamol for high fever. Aspirin, Ibuprofen are contraindicated
3. Nutritional support
4. Advice about warning signs and symptoms of shock
5. Follow-up preferably everyday till febrile for 24 hours

Without Shock

WHO criteria for DHF

- Acute sudden onset of high fever for 2-7 days
- Hemorrhagic manifestations with at least a positive Tourniquet test
- Platelet count, 100,000/cumm
- Hemoconcentration or other evidence of plasma leakage (ascites, pleural effusion)

Dengue Shock Syndrome

All criteria for DHF plus signs of circulatory failure

- Rapid and weak pulse
- Narrow pulse pressure (≤ 20 mm Hg) or hypotension for age
- Prolonged capillary refill, cold and clammy skin and restlessness

Not all patients need to be hospitalized

Indication for Admission

1. Excessive family concern or cannot be followed up
2. Poor oral intake
3. Spontaneous bleeding
4. Plt Count <1 lakh or rising Hematocrit 10-20%
5. Severe abdominal pain/vomiting

If signs of shock admit immediately

Volume Replacement in DSS

RL/NS 10-20 ml/kg/hr fast as possible

Shock persists
Colloidal plasma solution /plasma expander
(10-20 ml/kg/hr)

No improvement—suggestive of significant internal bleeding

Fresh whole blood

Improvement

Reduce IV fluids

6ml/kg/hr fluids

Hematocrit/vitals/urine output

Improvement → 5 ml/kg/hr → 3 ml/kg/hr → Continue for 24-48 hrs
Stop IVF when vitals stabilize

No improvement → 10/ml/kg/hr → 15/ml/kg/hr → Unstable vitals

10/ml/kg/hr → improvement → 5 ml/kg/hr

High hematocrit → Colloids

Low hematocrit → Blood transfusion

Improvement

Treatment of Complications

Blood and Platelet transfusion:

Blood transfusion indicated if

- Significant blood loss >10%
- Hemolysis
- Concealed internal bleeding

Platelet transfusion indicated if

- Significant bleeding with
- Thrombocytopenia
- Platelet count <10000/cu mm

Other complications to be taken care of:

- Electrolyte imbalance
- Fluid Overload
- Pleural effusion, ascites

Table 53.2: World Health Organization (WHO) grading of severity of dengue illness

Illness	*Grade*	*Symptoms*	*Laboratory*
DF		Fever with two or more of following signs: headache, retro-orbital pain, myalgia, arthralgia	Leukopenia, occasionally. Thrombocytopenia may be present, no evidence of plasma loss
DHF	I	Above signs plus positive tourniquet test	Thrombocytopenia < 100,000. Hematocrit rise > 20%
DHF	II	Above signs plus spontaneous bleeding	Thrombocytopenia < 100,000. Hematocrit rise > 20%
DHF/DSS	III	Above signs plus circulatory failure (weakpulse, hypotension, restlessness)	Thrombocytopenia < 100,000. Hematocrit rise > 20%
DHF/DSS	IV	Profound shock with undetectable blood pressure and pulse	Thrombocytopenia < 100,000. Hematocrit rise > 20%

DF : dengue fever (Flow chart 53.1)
DHF : dengue hemorrhagic fever
DHF Grade III or IV are also called DSS: Dengue shock syndrome

Laboratory Investigations

Table 53.3: Laboratory investigations viral hemorrhagic fevers

Investigations	*Day* 1-2	*Day* 3-4	*Day* 5-6	*Day* 10+
Hematological				
Hematocrit	N	↑	↑↑	N
Platelet count	N/↓	↓↓	↓↓	N
Differential count				
neutrophils	N	↓	N	N
lymphocytes	N	↑	↑↑	N
eosinophils	N	N	N	N
Coagulation profile				
Prothrombin time,	N	N/↑	↑/N	N
Activated partial thromboplastin time, Fibrinogen and Fibrin degradation products, Factors II, V, VIII, IX, X	N	N/↓	N/↓	N
Bone marrow	N	↓	↓/N	↑
Biochemical				
Serum protein (albumin)	N	↓	↓↓	↓
Transaminases AST ALT	N	N/↑	↑/N	N
Serum. Na, Cl	N	↓	↓	N
Urine (albumin)	+	+	+	N

Major hematological and biochemical abnormalities, including abnormalities in coagulation profile are listed in Table 53.3. Serological diagnosis of these fevers depends on the presence of IgM antibody or a rise in IgG antibody titres in paired acute and convalescent sera. All these flavi viruses share group antigens that can cross react in serological tests, complicating diagnosis. Virus isolation methods are not routinely used for diagnosis as they are expensive and not widely applicable.[11,12] Reverse transcriptase polymerase chain reaction (PCR) and hybridization probes for nucleic acid can detect virus.[13] IgM antibody becomes detectable during the acute phase of the illness and 90 percent of patients are IgM positive by the sixth day after the onset of symptoms. In primary dengue, IgG antibody begins to appear by the fifth day after the onset of symptoms. Titres rise slowly for weeks and then remain detectable for many years. In secondary or repeat infection IgG antibody is already present and titres rise rapidly over a few days. Other important hematological findings include leukopenia, hemoconcentration and thrombocytopenia.[14] Liver enzymes aspartate (AST) and alanine (ALT) transaminases are elevated.[15] There may be evidence of disseminated intravascular coagulation in severe cases. Chest radiograph may reveal pleural effusion ranging from mild to massive effusion. Reason for increased effusion observed on the right side is not clear. Ultrasound may in addition show pericardial effusion, ascites and gallbladder wall thickening.[16,17]

Management in the PICU

Indications for admission to PICU have been outlined earlier in section on clinical features. Contagiousness requires isolation in some cases. Rapid diagnosis is essential, and specimens must be handled according to biohazard precautions.

Therapy will have to be symptomatic and supportive, focusing on maintenance of circulation and vital organ function, adequate hydration, nutritional support, antibiotics and antimalarials in selected cases. So far established specific therapies are lacking. Ribavirin has been of some benefit at least in Lassa and Rift Valley fever, and serum from reconvalescents has been successfully used in Ebola patients.[1]

Fluid therapy is an essential component of therapy. Antipyretics may help to relieve the symptoms of dengue fever, but to avert Reye's syndrome and hemostatic complications, aspirin should not be used. Attentive clinical monitoring of suspected VHF cases and anticipatory and supportive care are life saving and have reduced the fatality rates by 50 to 100 fold. A treatment algorithm and a protocol for monitoring circulation and vascular leakage every 1 to 2 hours with serial clinical assessment of pulse, blood pressure, skin perfusion, urine output and hematocrit to trigger intravenous fluid therapy should be followed (see appendix). A greater than 20 percent hematocrit increase indicates a significant loss of intravascular volume (Hemoconcentration) and urgent need for fluid resuscitation.

Initial Fluid Resuscitation

Initial resuscitation should be rapid and aim to restore blood pressure and to reduce tachycardia. For Initial therapy, the type of fluid is not crucial: crystalloids or colloids may be used. Often 60-100 ml/kg may be necessary.[18-20] Ongoing capillary leak and vasodilator mediators lead to intravascular hypovolemia. Volume status is best assessed by central venous pressure (CVP). Echo-cardiography can also be used, if available to assess atrial size (collapsing/small atrium indicating hypovolemia).

The only limitation to volume administration is persistent elevation of filling pressures without an increase in cardiac output or blood pressure following volume administration. At this stage further fluid administration will not increase peripheral perfusion and by increasing venous pressure and tissue edema, decrease perfusion to myocardium and other tissues. Increased venous pressure increases vascular leaks, leading to pleural effusion, ascites, occasionally pericardial effusion and pulmonary edema. At this stage inotropic agents should be introduced to improve myocardial contractility and cardiac output. Dopamine is the most commonly used inotrope. In moderate doses increased inotropy, stroke volume and cardiac output occurs. Initial starting dose is 5 to 10 micrograms/kg/min titrated up or down according to clinical response with respect to blood pressure, capillary perfusion and heart rate. Dobutamine is an excellent inotrope but causes peripheral vasodilation, pulmonary vasodilation and tachycardia necessitating adequate volume status, as a prerequisite to its use. Use of dopamine in doses higher than 10 micrograms/kg/min requires use via a central line due to higher chances of skin necrosis when used via a peripheral vein due to intense vasoconstriction. If despite adequate volume resuscitation and administration of dopamine and dobutamine in moderate doses (15 microgram/kg/min each), clinical response is unsatisfactory, adrenaline infusion may be required. Adrenaline is a potent beta and alpha receptor stimulant which increases cardiac index and oxygen delivery. Initial starting dose is 0.05–0.2 microgram/kg/min titrated up to a maximum dose of 1 microgram/kg/min. Adrenaline infusion in high doses causes intense renal and splanchnic vasoconstriction resulting in decreased gut, liver and renal perfusion. However, in an adequately volume resuscitated patient with shock and poor renal perfusion due to low cardiac output, adrenaline infusion results in net improvement in renal blood flow by improving the cardiac output. Fortunately, in most patients volume resuscitation alone or volume resuscitation in combination with dopamine and dobutamine is able to achieve clinical improvement.

Fluids Used in Volume Replacement

Normal saline or Ringers lactate are used as crystalloids. They are cheap, readily available and provide quick, though transient intravascular expansion. These solutions not only replenish volume but also correct sodium loss. The major complication associated with the use of crystalloid solutions is either underhydration due to inadequete volume replacement or overhydration resulting in hypervolemia. Pulmonary edema is however rare in children unless gross overinfusion has occurred. The end point of volume replacement with hemodynamic monitoring is to maintain CVP within normal range. Colloids (hemaccel, hetastarch, dextrans) are expensive. Colloids, because of their increased oncotic pressure and very low permeability through capillary walls, produce quick volume expansion, as well as sustained increase in cardiac output. Disadvantages of colloids include chances of anaphylaxis. In addition, they may initiate or worsen the acute respiratory distress syndrome (ARDS). Dextrans inhibit platelet adhesion and aggregation. At our institution we use combination of colloids (fresh frozen plasma, blood, platelet concentrates, starch solutions such as hemeccel and Heta starch (HES), in conjunction with crystalloids such as ringers lactate or normal saline resulting in quicker restoration of blood volume, a more rapid rise in cardiac output, blood pressure, and a quicker improvement in tissue perfusion.

Monitoring of Shock

All children should be thoroughly examined clinically and fluid requirements should be calculated on hourly or 2 hourly basis and not on 12 hourly basis. Irritability and decreasing consciousness, poor urine output (< 0.5 ml/kg) and poor peripheral perfusion (rapid thready pulse, capillary filling time > 5 sec) are signs of deterioration. Intravenous access with at least two wide bore cannulae is necessary. Mean arterial blood pressure should be measured by intraarterial canulation. Central venous pressure (CVP) catheter placement is essential to allow for the infusion of vasoactive drugs and to estimate left ventricular end diastolic volume. Double lumen (size 4 french, 5 french outer diameter) or triple lumen central catheters (5 french, 5.5 french) are useful for multiple drugs as well as rapid fluid infusion. Gastric intramucosal pH may be used as a measure of splanchic hypoperfusion. Lactate concentration is also increased with inadequate perfusion and anaerobic glycolysis. Echocardiography is non-invasive way of knowing about systolic and diastolic function, presence of pericardial effusion and an estimate of pulmonary artery pressure.

Management of Hemorrhage

The mere occurrence of thrombocytopenia does not merit platelet infusions.

Patients usually do not have clinical bleeding unless platelet counts are less than 20-30000/cu mm. However platelet transfusion can increase the platelet count.

Ordinarily one unit of platelets in an adult should produce a rise in platelet count by 5000-10000/cu mm. If this increase is not observed, platelets obtained from HLA matched donors, other single matched donors, or platelets on cell separator from family donors may be given. In most severe cases of viral hemorrhagic fevers with disseminated intravascular coagulation, which is observed in intensive care settings, bleeding is invariably present. The patients show a prolonged prothrombin time and activated partial thromboplastin time, thrombocytopenia, hypofibrinogenemia and increase in fibrin degradation products. The presence of crosslinked fibrin as judged from a positive D-dimer test also points to disseminated intravascular coagulation. Serious bleeding is countered by fresh blood transfusion and or by transfusions of fresh frozen plasma in sufficient quantity so as to decrease the prothrombin time to within 2-3 seconds of normal.[21] Cryoprecipitate may be infused to maintain fibrinogen levels above 100 mg/dl, and platelet concentrates and platelets on cell separators given to raise the platelet count > 50000/cu mm. Vitamin K deficiency coexists in severely ill patients, because of involvement of liver. Vitamin K should also be administered if prothrombin time is prolonged.

Respiratory Support

Increased work of breathing increases oxygen consumption and leads to lactic acidosis. Early use of CPAP or NIPPV (Non-invasive mechanical ventilation), removes the work of breathing and causes redistribution of cardiac output to vital organs. This also allows for maintaining acid base balance. Early endotracheal intubation and initiation of mechanical ventilation is mandatory in severely hypoxemic children despite maximal oxygen therapy. Sedation and muscle relaxation for endotracheal intubation should be cautiously used. Ketamine sedation (maintains blood pressure in hypovolemic patient) and succinyl choline muscle relaxation is a good combination for facilitating endotracheal intubation. Once intubated, midazolam (0.1 mg/kg) and a longer acting muscle relaxant such as vecuronium (0.1 mg/kg) can be used for maintaining sedation and muscle relaxation. Both midazolam and vecuronium can be used as a continuous infusion. In younger children sedation with midazolam infusion alone is sufficient. However, with older children and all patients with low pulmonary compliance due to pulmonanry edema and pleural effusion a continuous infusion of vecuronium may be required to achieve better ventilation by overcoming chest muscle tone and abolition of spontaneous breathing. Pancuronium is an equally good and cheaper agent compared to vecuronium, except that it can cause excessive tachycardia.

Once patient is stabilized and well sedated invasive lines such as CVP, and arterial lines can be inserted by person most experienced in these procedures to minimize procedure related blood loss due to low platelet count and hematoma formation. Sedation is particularly useful in young, anxious and uncooperative children.

Acute Respiratory Distress Syndrome (ARDS) in VHF

Because vascular integrity is usually restored spontaneously in 48 hrs, overhydration resulting in pulmonary edema is a risk. As a result of already existing risk of acute respiratory distress syndrome due to capillary leak and excessive fluid administration, respiratory distress syndrome in hospitalized children has been reported from Malaysia and elsewhere.[22,23] Therapy of ARDS aims at maintaining tissue oxygen delivery. To attain this on a nontoxic level of FiO_2, mechanical ventilation with positive end expiratory pressure (PEEP) is used.[24] Levels of PEEP usually required range from 4 cm of water to 8 cm of water. Best level of PEEP is that which allows adequate tissue O_2 delivery at a nontoxic level of FiO_2. Potential adverse effects of PEEP include pulmonary barotrauma and air leak, increasd air trapping with CO_2 retention, inhibition of cardiac contractility by cardiac tamponade effect. Use of PEEP in individual patients requires careful, sequential observation of both respiratory and cardiac function, as the PEEP is increased in increments of 2-3 cm of water.[25] If cardiac output is decreased by PEEP indicated by decreased peripheral perfusion and decreasing blood pressure, then cardiac function should be supported with fluids and or inotropic agents. Swan Ganz pulmonary arterial catheter insertion for cardiac output monitoring may be ideal but is not practical due to availability of indirect but safer clinical indicators of cardiac output as well as echocardiography to assess volume status and ejection fraction. During attempts to decrease PEEP, hypoxemia may recur, and to prevent this following conditions should be met before PEEP is weaned down: Patient should be stable, at FiO_2 less than 0.4 with PaO_2 at least 80 mmHg, stable or improving for 12 hours with improving pulmonary compliance (lowered peak airway pressure on the same tidal volume).[26]

Strategy for Mechanical Ventilation

No ventilatory approach has been found superior to the ventilation strategy using low tidal volume with permissive hypercapnea.[27] At initiation of ventilation a tidal volume of 6-8 ml/kg, FiO_2 of 1, and rate appropriate to age is used. After evaluation of gas exchange, therapy is adjusted with gradual increase of PEEP and decrease of FiO_2. With severe ARDS and very high peak airway pressures, considerations can be given to using lower tidal volumes and faster ventilation to achieve similar alveolar ventilation. $PaCO_2$ up to 55 to 60 mm of mercury can be allowed as long as the pH stays above 7.20 and PaO_2 greater than 60 mm of mercury with absence of metabolic acidosis. As mentioned earlier, sedation and neuromuscular blockade should be used to decrease the work of breathing and patient ventilator dyssynchrony. Once the compliance of lungs improves indicating reduction in interstitial pulmonary edema as well as reduction in pleural fluid as supported by chest radiograph, weaning from ventilation can be initiated. A negative fluid balance is another factor supporting overall improvement as indicated by almost simultaneous diuresis as capillary leak begins to heal. Sedation and muscle relaxation can be reduced and gradually discontinued and patients ventilator setting can be changed to SIMV (Synchronized intermittent mechanical ventilation) volume control with pressure support ventilation, once spontaneous breathing effort is detected. As a mandatory prerequisite to weaning from mechanical ventilation, hemodynamic status must be stabilized and patient should be on none or minimal inotropic support.

Most patients can be weaned off and extubated within 24 to 48 hours of initiation of weaning. Individual patients may have slower weaning based on severity of lung disease.

Use of Steroids and Other Modalities

Neither high dose methylprednisolone (30 mg/kg)[28] norAC-17 (carbazochrome sodiumsulfonate),[29] which was believed to reduce vascular permeability, was beneficial in controlled trials. In some institutions, intravenous gamma globulin has been used empirically but no benefits have been established. Desmopressin has also been used in one study[29] without much benefit.[30]

Prognosis

Prognosis of uncomplicated dengue fever is generally good, however VHF with shock (DSS) and disseminated intravascular coagulation carries a potentially poor prognosis and mortality depends on severity of illness, presence of shock as well as early transfer to tertiary care center and institution of aggressive intervention in pediatric intensive care unit. In expert hands the mortality of VHF has dropped from as high as 44 percent to as low as 0.2 percent. In DSS, however, with bleeding manifestation and ARDS, the overall mortality can range from 40 to 60 percent. In a recent multicenter ARDS net study, use of low tidal volumes ventilation strategy was associated with as low as 40 percent mortality in all patients with ARDS (not dengue related ARDS).[27]

SUMMARY

VHF is a common clinical entity with a significant percentage of cases presenting with frank hemorrhagic manifestations and shock. Early detection of potentially sick children (patients with tachycardia, poor capillary refill, respiratory distress and deteriorating mental status with or without hypotension) and prompt referral to tertiary level PICU is crucial to avoid poor outcome. Management in the PICU is supportive. Close monitoring of respiratory and hemodynamic status is essential to guide therapy. Most patients can be treated with aggressive fluid therapy and close clinical monitoring. Initial therapy with crystalloid containing fluids followed by colloids (hemeccel and hetastarch) well tolerated. Coagulation abnormalities can be managed with fresh frozen plasma, vitamin K and platelet transfusions as necessary.

DSS presenting with ARDS, carries a potentially poor prognosis if not promptly detected and treated. Patients with shock and ARDS require early mechanical ventilatory support with low tidal volume, best PEEP as well as adequate inotropic support. Recent improvement in mortality has resulted from better understanding of supportive measures and safer strategies of conventional mechanical ventilation.

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APPENDIX
IAP INTENSIVE CARE CHAPTER DENGUE GUIDELINES 2008 FOR MANAGEMENT OF DENGUE HEMORRHAGIC FEVER (DHF) AND DENGUE SHOCK SYNDROME (DSS)

INTRODUCTION

Dengue is a mosquito borne viral illness. Dengue epidemics have been known since last 300 years. First confirmed epidemic was reported from Philippines in 1953-1954. Since then Southeast Asia is experiencing major outbreaks with increasing morbidity and mortality. Some countries are having dengue outbreaks every year. World-wide 2.5 billion people are at risk and 50-100 million cases are being reported annually. Each year approximately 5,00,000 cases of Dengue hemorrhagic fever (DHF) (Fig. 53.1) require hospitalization, including 90% children less than 15 years of age. Mortality of Dengue hemorrhagic fever is approximately 5% with 25,000 deaths reported each year. India, Sri Lanka and Myanmar are hyperendemic for Dengue fever because of significant increase in the proportions of dengue cases with severe disease.

Usually it is considered an urban disease but now it is spreading in rural areas also. All Socio-economic groups are affected.

Factors associated with resurgence of Dengue epidemics:

1. Unprecedented growth of human population.
2. Unplanned and uncontrolled urbanization.
3. Inadequate waste management and water supply.
4. Increased distribution and densities of vector mosquitoes
5. Lack of effective mosquito control measures.
6. Increased movement and spread of dengue virus.

Dengue and dengue hemorrhagic fever are caused by Dengue Virus. This is an arbovirus, flavivirus and is composed of single-stranded RNA. It has 4 serotypes (DEN-1, 2, 3, 4). DEN-2 was the predominant serotype in the 1980s and the early 1990s in recent years it has changed to the DEN-3 serotype.

It is transmitted by mosquitoes Aedes mosquito. *Aedes aegypti* is the most important epidemic vector. A albopictus and A polynesiensis may act as vectors in some geographic locations. Widespread abundance of *Aedes aegypti* is seen in at-risk areas. Vertical transmission from mother to child has been reported.

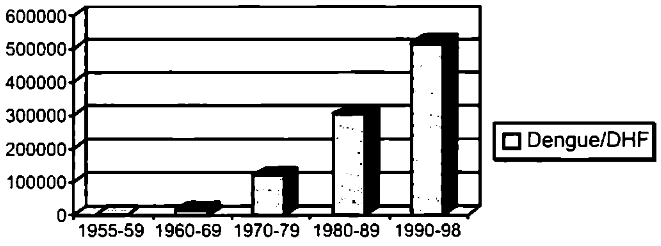


Fig. 53.1: Dengue/DHF, average annual number of cases of reported to WHO,1955-98

Host factor: Dengue virus infects humans and lower primates. Man is considered as its urban reservoir. Studies in Africa and Malaysia demonstrated that monkeys are infected with Dengue virus and are the likely reservoir hosts.

RISK FACTORS REPORTED FOR DHF

Virus strain
Pre-existing anti-dengue antibody previous infection maternal antibodies in infants
Host genetics
Age
Higher risk in secondary infections
Higher risk in locations with two or more serotypes circulating simultaneously at high levels (hyperendemic transmission)

PATHOGENESIS OF DENGUE AND DHF (FIG. 53.2)

Pathogenesis is not fully understood. It is hypothesized that there is antibody-dependent enhancement of virus multiplication in macrophages by heterotypic antibodies which were formed during previous dengue infection. Antibody-dependent enhancement is the process in which certain strains of dengue virus, complexed with non-neutralizing antibodies, can enter a greater proportion of cells of the mononuclear lineage, thus increasing virus production.

Infected monocytes release vasoactive mediators, resulting in increased vascular permeability, third spacing of fluids and hemorrhagic manifestations that characterize DHF and DSS (Dengue shock syndrome).

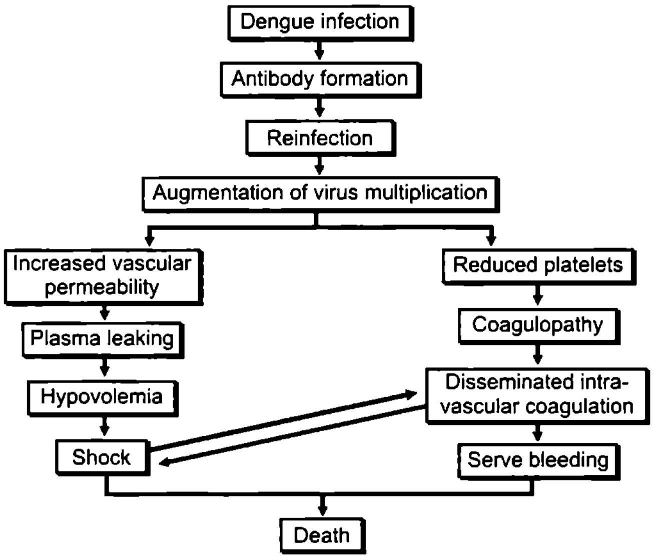


Fig. 53.2: Pathogenesis of Dengue shock syndrome (DSS) and DHF (Dengue hemorrhagic fever)

Mechanism of Thrombocytopenia

- Bone marrow suppression
- Immune injury – sequestration in reticuloendothelial cells
- *In vitro* – aggregation at endothelial cells
- Platelet lyses
- DIC (Disseminated intravascular coagulation)
- Decreased platelet survival

CLINICAL CLASSIFICATION

Dengue viral infection (Fig. 53.3) has three main clinical manifestations:

1. Undifferentiated febrile illness (UF) or viral syndrome
2. Dengue Fever (DF)
3. Dengue Hemorrhagic Fever (DHF)

DENGUE FEVER

An acute onset febrile illness of 2-7 days duration with two or more of the following:

Headache
Retro-orbital pain
Myalgia/arthralgia
Rash- macular papular
Petechiae and positive tourniquet test. (Hemorrhagic manifestation are uncommon).
Leukopenia

Flushing, a characteristic feature is commonly observed on the face, neck, and chest. Coryza may also be a prominent symptom especially in infants. Younger children tend to present with coryza, diarrhoea, rash and seizure, and less commonly with vomiting, headache, and abdominal pain.

DENGUE HEMORRHAGIC FEVER (DHF)

DHF usually follows secondary dengue infections, but may sometimes follow primary infections, especially in infants. In such infants, maternally acquired dengue antibodies are presumed to enhance primary infections. DHF is characterized by high fever, hemorrhagic phenomena, and features of plasma leakage (Table 53.4).

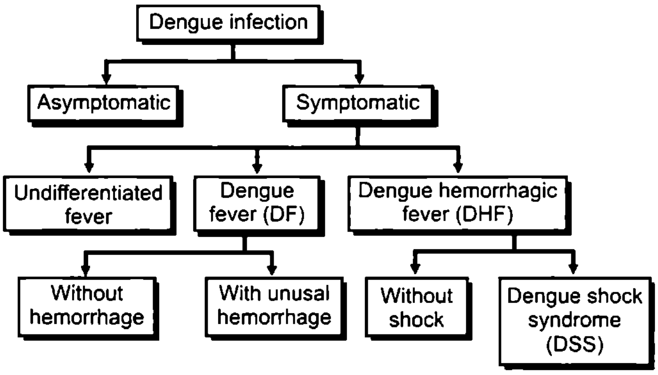


Fig. 53.3: Dengue infection

Table 53.4: Clinical Features of DHF

General

- High fever, intermittent.
- Severe headache (especially retro-orbital).
- Flushing.
- Myalgia and arthralgia.
- Vomiting.
- Anorexia.
- Acute abdominal pain.

Bleeding manifestations

- Epistaxis.
- Bleeding from gums.
- Petechiae and eccymoses.
- Hematemesis and melena.
- Spotting or menorrhagia in females.

Features of plasma leakage

- Circulatory disturbances (low blood pressure, tachycardia, narrow pulse pressure, and poor capillary refill time).
- Polyserositis (pleural effusions, ascites sometimes pericarditis).

Complications

- Encephalopathy and encephalitis.
- Liver failure.
- Myocarditis.
- Disseminated intravascular coagulation leading to massive bleeding.

Hemorrhagic tendency is evidenced by one or more of following:

- Positive tourniquet test
- Petechiae, ecchymosis or purpura
- Bleeding from mucosa (mostly minor—epistaxis or bleeding from gums), injection sites, etc.
- Hemetemesis or melena.

Tachycardia and hypotension characterize the onset of plasma leakage. Evidence of plasma leakage manifested by one or more: 20% rise in hematocrit, > 20% drop in hematocrit following fluids, or signs of plasma leakage (pleural-effusion, ascites or hypoproteinemia). Pleural effusions are usually seen on the right side; a right decubitus chest radiograph is best for detecting small effusions. Abdominal ultrasound scans may demonstrate ascites or a thickened gallbladder wall. Pericardial effusions may also occur.

In mild to moderate cases: Fever subsides with profuse sweating. Mild changes in pulse rate and blood pressure may be noticed with cold extremities and skin congestion. Patient recovers spontaneously or after fluids and electrolyte therapy.

In severe cases: Sudden deterioration may occur after few days. Fever subsides in 3-7 days and signs of circulatory collapse appear. Signs of plasma leak, acute abdominal pain are noticeable. Consciousness is usually intact but episodes of dizziness may indicate postural hypotension. Patient should be hospitalized for fluid therapy and close monitoring. Patient may die of profound shock if untreated. Survivors recover within 2-3 days. During convalescent stage, bradycardia or arrhythmia may be noted.

WHO defines a case of DHF as follows:

A patient with the following four criteria:

1. Acute sudden onset of high fever for 2–7 days.
2. Hemorrhagic manifestations with at least a positive tourniquet test.
3. Platelet count <100,00/cuml.
4. Hemoconcentration (rising packed cell volume) > 20% or other evidence of plasma leakage—for example, ascites, pleural effusions, low level of serum protein/albumin.

In DHF, bleeding may not correlate with the platelet counts and usually occurs once the fever has settled. Vaginal bleeding is commonly reported in females.

Convalescence in DHF is usually short and uneventful. The return of appetite is a good indicator of recovery from shock. Bradycardia is also seen in this period. If present, a confluent petechial rash with erythema and islands of pallor (usually known as a recovery rash) is characteristic of dengue infections. During the convalescent stage, many patients also complain of severe itching especially on the palms and soles.

DENGUE SHOCK SYNDROME (DSS) (FLOW CHART 53.2)

All of the above criteria of DHF plus signs of circulatory failure manifested by:

Rapid and weak pulse

Narrow Pulse pressure (≤ to 20 mm Hg) or Hypotension for age

Prolonged capillary refill, Cold and Clammy skin and restlessness

Severity of DHF

WHO classification of DHF / DSS

Grade I	Fever, only positive tourniquet test, No shock
Grade II	No shock, has spontaneous bleeding other than positive tourniquet test.
Grade III	Shock , Hypotension (Pulse pressure < 20 mm Hg)
Grade IV	Profound shock with unmeasurable blood pressure and/or pulse.

Every DSS patients must have evidence of plasma leakage and thrombocytopenia (platelet count < 100,000 cells/cumm). Hypotension (Pulse pressure less than 20 mm Hg)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

A high index of suspicion is needed. Diagnosis should be considered in any acute febrile illness.

During the early febrile phase it may mimic a spectrum of febrile illnesses including viral hemorrhagic fevers, malaria, leptospirosis (Table 53.5). During febrile phase, the clinical presentation of both DF and DHF are almost the same. Once a febrile, DF patients will recover rapidly, DHF patients continue to look sick and may rapidly worsen to stage of shock.

Diagnosis – Dengue Fever

Acute onset of high fever for 1-2 days, finding of flushed face without coryza or any other respiratory—suggest the possibility of dengue infection.

Table 53.5: Differential diagnosis of dengue fever and DHF

Dengue Fever

- Infectious mononucleosis.
- Chickengunya viral infections.
- Coxsackie and other enteroviral infections.
- Rickettsial infections.
- Rubella.
- Parvovirus B19 infections.
- Leptospirosis.
- Influenza.
- Measles
- Rubella
- Malaria
- Typhoid fever
- Meningococcemia
- Rickettsial infections
- Bacterial sepsis

DHF

- Leptospirosis.
- Chikengunya viral infections.
- Kawasaki disease.
- Yellow fever.
- Hanta viral infections.
- Other viral haemorrhagic fevers.
- Meningococcal septicemia.

A positive tourniquet test (Inflate blood pressure cuff to a point midway between systolic and diastolic pressure for minutes. Positive test: > 10 petechiae per 2.5 cm^2) increases probability. Test is Positive in—50% on 1st day, to over 80% by the end of febrile phase.

Enlargement of liver, soft and tender, supports a clinical diagnosis.

Platelet count drops shortly before or simultaneously with a rise in Hct.

Diagnostic Value of Signs

High fever and flushed face without coryza

	Sensitivity	Specificity
First day	73.3	93.3
Second day	90.5	89.2
Third day	85.5	87.9

Tourniquet test

	Sensitivity	Specificity
First day	53.3	75.8
Second day	90.6	77.8
Third day	98.7	74.2

Positive tourniquet or petechiae and leukopenia (WBC ≤ 5,000 cells/ cumm)—DF with a positive predictive value of 83%.

Diagnosis of DHF: Clinical Criteria

Acute sudden onset of high fever 2-7 days.

Hemorrhagic manifestations at least a +ve tourniquet test.

Hepatomegaly.
Circulatory disturbance or shock.
Laboratory criteria
Platelet count < 100,000 cells/cumm.

Hemoconcentration (rising Hematocrit >20%) or other evidences of plasma leakage, e.g. ascites, pleural effusion, low level of serum protein/albumin/cholesterol.

Unusual Manifestations—Complications

Central nervous system involvement
Usually lethargy, confusion, consciousness/coma, nuchal rigidity,
Convulsion, Paresis
Frequently associated with:
Prolonged shock with metabolic acidosis
Severe DIC that leads to intracranial bleeding.
Electrolyte imbalances, e.g. hyponatremia, hypocalcemia.
Metabolic disturbances, e.g. hypoglycemia.
Encephalopathy associated with acute hepatic failure or Reye's syndrome.
In general, CNS involvement is consistent with encephalopathy. True encephalitis is very rare.

Acute Hepatic Failure (AHF)

AHF is a problem of concern associated with high mortality. Likely multifactorial causes and/or contributing factors:

Hepatocyte damage possibly caused directly by Dengue virus.

Presents with rapid change in the conscious with rising, high level of liver enzyme

Rapid recovery in those who survive are more suggestive of Reye's syndrome than viral hepatitis.

Renal Failure

Kidneys - rarely affected in DSS. Most reported cases are associated with late acute hepatic failure.

The risk factors are use of nephrotoxic drugs, intravascular hemolysis e.g. G-6-PD deficiency, and abnormal hemoglobinopathy.

Myocardial Dysfunction

Decreased ejection fraction, and LV performance indices.

Dual infections with—concurrent leptospirosis may be associated with ARF.

Causes of Death in DHF

Prolonged shock,
Massive bleeding,
Fluid overload and
Acute hepatic failure with encephalopathy.
With shortage of experienced medical team, the case fatality rate is high.

LABORATORY METHODS FOR DIAGNOSIS

For individual patient clinical diagnosis is adequate for starting treatment. The tests available for laboratory diagnosis are shown in Table 53.6.

Virus Isolation: By Cell Culture and Fluorescent Antibody Test is not needed for routine diagnosis but it is needed to determine serotype of the infecting virus for research and epidemiological studies

IgM ELISA test for serologic diagnosis has sensitivity ranging from 83.9–98.4% and a specificity of 100%.

On hemagglutination inhibition (HI) test, a fourfold or greater rise in antibody titres is suggestive of a flavi virus infection (and not diagnostic of dengue infections). However, a single antibody titre >1/2560 is accepted as indicator of secondary dengue infection if supported by a clinical history suggestive of dengue.

RT-PCR is useful for early detection of dengue infection when antibodies are not yet detectable. It is more sensitive than virus isolation, allows for rapid detection within 24 hours. It is useful for epidemiological studies as dengue serotypes could be identified without cross reactivity with other flavi viruses.

A confirmed case is a patient who has positive viral identification and/or a serological test. HI antibody > 1,280 or positive IgM/ IgG ELISA test in convalescence serum is diagnostic.

MANAGEMENT: FEBRILE PHASE

1. Rest, oral fluids
2. Reduction of fever
   Tepid sponge after a dose of paracetamol
   Antipyretic – only paracetamol 10 mg/kg/day for high fever > 39°C, 4-6 hours
   Aspirin, ibuprofen are contraindicated due to interference with platelet function.
3. Nutritional support
   Soft, balanced-nutritious diet, juice and electrolyte solution. Plain water is not adequate. Avoid black or red color food or drinks (may cause confusion with bleed).
4. ***Other supportive and symptomatic treatment***:
   - Domperidone—1 mg/kg/day in 3 divided doses if severe vomiting for 1-2 days. One single dose may be adequate.
   - Continue anti-convulsant—if the patient on febrile convulsion therapy.
   - H_2-blockers(ranitidine) —recommended if GI bleeding.
5. ***Antibiotic***—not necessary it may lead to complications.
6. ***Steroid is ineffective*** in preventive shock DHF. It may harm by causing stress ulcer and massive GI bleeding.
7. Advise should be given about warning signs and parents should be asked symptoms of shock should be asked to report immediately if any of the following is present.
   - Clinical deterioration when defervescence (no fever or fever).

Table 53.6: Tests for Laboratory diagnosis of dengue infections

Virus isolation
- Mosquito cell lines.
- Mosquito inoculation technique.
- Vertebral cell culture.

Serological diagnosis
- Haemagglutination inhibition test.
- ELISA.
- Complement fixation test.
- Neutralization test.
- Antigen capture enzyme immunosorbent assay.

Molecular diagnostic methods
- RT-PCR

  - Bleeding in any form
  - Severe vomiting / abdominal pain
  - Very thirsty
  - Drowsy, sleeping all the time.
  - Refuse to eat or drink
  - *Shock/impending shock*: Cold, clammy skin and extremities, Restless, irritable infant, Skin mottling, capillary refill time > 2 seconds, Decrease urine output or no urine for 4-6 hours, Behavior changes, e.g. confusion, fowl language.

8. ***Intravenous Fluids***: If any doubt, provide intravenous fluids, guided by serial hematocrits, blood pressure and urine output.

   The volume of fluid needed is similar to the treatment of diarrhea with mild to moderate isotonic dehydration (5%-8% deficit), just correct dehydration, and discontinue as soon as possible.
9. **Follow-up:** preferably everyday—from day 3rd of the illness until patient is a febrile for >24 hours. Important points to evaluate are:
   1. History of bleeding, abdominal pain, vomiting, appetite, intake and urine output.
   2. Physical examination: vitals signs, liver size and tenderness.
   3. CBC:WBC < 5,000 cells/cumm with lymphocytosis and increase in a typical lymphotocytes - and platelet counts < 100,000 cells/cumm - heralds entry to critical phase with rising Hct of 10-20% — indicates that the patient is in the critical period.
   4. *Liver function tests (LFT)*: Every patient who has change in consciousness, restlessness, confusion and irritable should have LFT.

High Risk Dengue Patients that Need Special Attention

1. Infants under 1 year of age
2. Prolonged shock (Grade IV patients)
3. Overweight/obese patients.
4. Massive bleeding
5. Change of consciousness, especially restless and irritable or coma
6. Have underlying diseases e.g. thalassemia, G-6-PD deficiency, heart disease.

Indication for Admission

There is no need to hospitalize all DHF patients: only about one-third will develop shock. Following patients need hospitalization:

1. Excessive Family concern or cannot be followed up.
2. Very weak, cannot eat or drink, Not drinking / Feeding poorly
3. Spontaneous Bleeding
4. Platelet counts ≤ 100,000 cells/ cumm and/or rising Hct 10-20%
5. Clinical deterioration when defervescence.
6. Severe abdominal pain/ vomiting

Hospitalization for bolus intravenous fluid therapy may be necessary where significant dehydration (>10% of normal body weight) has occurred and rapid volume expansion is needed.

Admit Immediately if signs of shock. These signs are as follows:

1. Rapid pulse with no fever
2. Capillary refill time > 2 seconds
3. Cold, clammy, skin, mottling restless
4. Narrow pulse pressure ≤ 20 mmHg, e.g. 100/80,
5. Hypotension
6. Oliguria, no urine for 4-6 hours.
7. *Change of consciousness*: Drowsy to stupor, restless, irritable (encephalopathy)

MANAGEMENT: CRITICAL PHASE

Adequate fluid administration, regular assessment of fluid and electrolyte balance, and monitoring for development of complications is vital. Vital signs should be monitored every 1-2 hours to detect early progression to shock. The hematocrit should ideally be monitored every 4-6 hours.

A. General Measures

1. Give oxygen via face mask/nasal cannula in every patient with shock/impending shock. Nasal CPAP is an effective treatment in acute respiratory failure associated with DSS (Grade B evidence).[1]
2. Frequent monitoring.
3. Stop bleeding with proper technique e.g. anterior nasal packing for massive epistaxis.
4. Avoid invasive procedures e.g. no NG tube insertion, no gastric lavage.
5. Essential nursing care.
6. Sedative is needed in some cases to restrain an agitated child. A single dose of chloral hydrate (12.5-50mg/kg), orally or rectally, is recommended. Long acting sedatives should be avoided. Restlessness may be associated with insufficient tissue perfusion, or may be an early sign of hepatic failure, these should be attended.

B. Monitoring of children DHF/ DSS

1. Vital signs every 15-30 minutes till stable, then 1-2 hourly
2. Hematocrit every 2 hr for 6 hr, then every 4 hr for till the patient is stable. Monitor 12 hourly during recovery.
3. Fluid balance sheet : type of fluid, amount, rate etc.
4. Accurate urine output
5. Serum electrolytes and blood gases every 12 hr.
6. DIC profile and liver function tests as and when indicated.
7. Weight every 12 hr.

C. Obtain Laboratory Tests

1. In uncomplicated DHF cases, Hct and platelet counts are the only 2 tests necessary.
2. In those at high risk of complicated DHF.
   a. Blood grouping/matching
   b. Blood sugar
   c. Blood electrolyte (Na, Ca, K, CO_2)
   d. Liver function test
   e. Renal function test (BUN, Creatinine, uric acid)
   f. Blood gas
   g. Coagulogram (PTT, PT, TT)

D. Intravenous (IV) Fluids

The only known effective treatment in DSS is timely, aggressive fluid resuscitation. For children with DHF III there is no evidence that colloids are superior to crystalloids for initial resuscitation (Grade A evidence). No study has directly investigated whether colloids offer an advantage to crystalloids in patients with severe DHF III (pulse pressure <10 mmHg) or DHF IV. With appropriate use of fluid resuscitation in DSS mortality rates have been shown to be <0.2%.

NCPAP is effective in children with DSS complicated by acute respiratory failure.

For IV access large peripheral vein should be used, insertion of central venous line carries the risk of hemorrhage. The intraosseous route is acceptable in the child with profound shock.

1. IV fluids should be given only when patient is entering the critical period: thrombocytopenia ≤100,000, rising Hct 10-20%.
2. *IV fluids before critical phase cannot prevent shock but may cause fluid overload.*
3. Early detection of shock is most important. Prolonged shock will trigger more advanced DIC and acidosis, massive bleeding and Multiorgan failure (MOF) later.
4. *Type of IV fluid used* (Isotonic salt solution): Fluids used for rapid volume expansion include the following:
   - Normal saline, Ringer's lactate or Ringer's acetate.
   - Colloidal solution: Plasma, plasma substitutes (e.g. Dextran 40) or 5% albumin (50 g/l)

   In young infants without shock-N/2 saline in 5% Dextrose. In initial resuscitation type of fluid had no effect on mortality and morbidity.[2-4]
5. Fluid replacement—minimum necessary to maintain effective circulatory volume, excess amount will leak into the pleural and peritoneal spaces
6. IV fluid: Initial rate of administration

   Shock patients:

   Grade III – 10 ml/kg/hour for 1-2 hours.

   Grade IV – Free flow or 20 ml/kg/dose IV bolus until BP can be measured (usually within 5-15 minutes), then reduce the rate to 10 ml/kg/hour for 1-2 hours.

   Non shock patients: Initial rate at maintenance or + 5% deficit and then reduce the rate to minimal after 2-4 hours if possible.

   Body weight < 15 kgs : rate 4-7 ml/kg/hour, Body weight 15-40 kgs : rate 3-5 ml/kg/hour

   Increase or decrease the rate of IV fluid depending on:

   Clinical signs: General conditions, capillary refill time, BP, Pulse rate, Respiratory rate and Temperature

   Hematocrit

   Urine output

   If No response to IV fluids:: Consider and correct

   Massive plasma leakage

   Concealed internal bleeding –decrease in Hct

   Hypoglycemia – Blood sugar < 60 mg%

   Hyponatremia, hypocalcemia – electrolyte

   Acidosis – on blood gas analysis metabolic acidosis.

   Colloidal solutions is used in patients who already had volume overload: massive pleural effusion. The initial rate is 10 ml/kg/hour. This will reduce the Hct about 10 points e.g. from 53% to 43%. After that reduce to 5, then 3 ml/kg/hour.

Continued replacement of further plasma loss: Duration of IV fluid is between 24-48 hours. Plasma loss may continue for 24-48 hours, requiring continued fluid administration. The administration of intravenous fluids should be discontinued when the hematocrit level falls to approximately 40%,with stable vital signs. Good urine flow indicates sufficient circulating volume. In general, intravenous fluid therapy is not be needed for more than 48 hours after the termination of shock. Reabsorption of extravasated plasma occurs(manifested by a further drop in hematocrit after intravenous fluids have been stopped), and hypervolemia, pulmonary edema or heart failure may be caused if more fluid is given. **It is extremely important that a drop in hematocrit at this later stage is not interpreted as a sign of internal bleeding.** Strong pulse and blood pressure and adequate diuresis are good signs at this stage. They rule out the likelihood of gastrointestinal hemorrhage, which is found mostly during the shock stage. The return of the patient's appetite is also a sign of recovery.

E. Blood and Platelet Transfusion

Blood transfusion is needed in 10% DHF patients. The indications are— significant blood loss >10% (6-8 ml/kg), hemolysis, concealed internal bleeding.

Fresh whole blood (FWB) 10 ml/kg/dose or packed red cell (PRC) 5 ml/kg/dose is given.

Platelet transfusion is indicated if there is significant bleeding with thrombocytopenia. Mild reductions in platelet counts are usually not associated with significant bleeding. Moreover, thrombocytopenia in DHF/DSS is short lived; platelets return to normal by 7-9 days. Platelet concentrate is indicated if platelet count is less than 10,000/mm^3 (10-20 ml/

kg of platelets). Only 0.4% of DHF patients need platelet transfusion.

Some seriously sick patients with bleeding and DIC have benefited from heparin therapy and Cryoprecipitate (1 unit per 5 kg body weight) followed by platelets (4 units/m^2 or 10-20 ml/kg) within one hour and fresh frozen plasma (FFP – 10-20 ml/kg). Frequent clinical assessment and regular coagulation profile (PT, aPTT, fibrinogen, platelet and FDP) are mandatory as indicated.

F. Treatment of Complications

1. *Electrolyte imbalance*
   Hyponatremia
   Hypocalcemia—from leakage of Ca. 10% Ca gluconate 1 ml/kg/dose, IV push slowly q 6 hrs.
2. *Fluid Overload:* The common causes are
   - Early IV fluid therapy—from febrile phase
   - Excessive Use of hypotonic solutions.
   - Non reduction the rate of IV fluid after initial fluid resuscitation.
   - Blood loss replaced by fluids in cases with concealed bleed.

   Use of judicious fluid removal using colloids with controlled diuresis (frusemide 1 mg/kg infusion over 4 hours) may decrease mortality rates in the severest forms of dengue shock syndrome.
3. *Large pleural effusions, ascites:*
   Careful titration of intravenous fluids will limit the accumulation of large pleural effusions, ascites and positive fluid balance in children. Large pleural effusions during the recovery phase after 48 hours may need small doses of frusemide (0.25-0.5mg/kg 6 hourly for 1 to 2 doses). Avoid insertion of intercostal drains and tracheal intubation. In patients with severe hypotension and hypoxemia with increased intra-abdominal pressure (IAP) due to massive ascites/ pleural effusions, drainage of ascites and mechanical ventilation may be life-saving.

Steroids have not been proven to beneficial in DSS but existing studies may have been underpowered to detect a treatment benefit[5,6] (Grade B evidence). **AC-17** has not been shown to be beneficial in DSS but the study was underpowered to detect a potential treatment benefit[7] (Grade B evidence).

SIGNS OF RECOVERY

Stable pulse, blood pressure and breathing rate
Normal temperature
No evidence of external or internal bleeding
Return of appetite
No vomiting
Good urinary output
Stable haematocrit
Convalescent confluent petechiae rash

CRITERIA FOR DISCHARGING PATIENTS

Absence of fever for at least 24 hours without the use of anti-fever therapy
Return of appetite, visible clinical improvement
Good urine output
Minimum of three days after recovery from shock
No respiratory distress from pleural effusion and no ascites
Platelet count of > 50,000/mm^3

WHAT NOT TO DO

Do not give Aspirin or Ibuprofen
Avoid giving intravenous therapy before there is evidence
Avoid giving blood transfusion unless indicated of need.
Avoid giving steroids
Do not use antibiotics
Do not change the speed of fluid rapidly

Blind Insertion of tubes is hazardous and is not recommended. Insertion of nasogastric tube carries the risk of trauma and hemorrhage to nasal passages and stomach. If a gastric tube is necessary, the oral route is preferable. Insertion of intercostal drains carries the risk of trauma and hemorrhage to the lung. Avoid insertion of intercostal drains and tracheal intubation.

PREVENTION AND CONTROL OF DENGUE FEVER

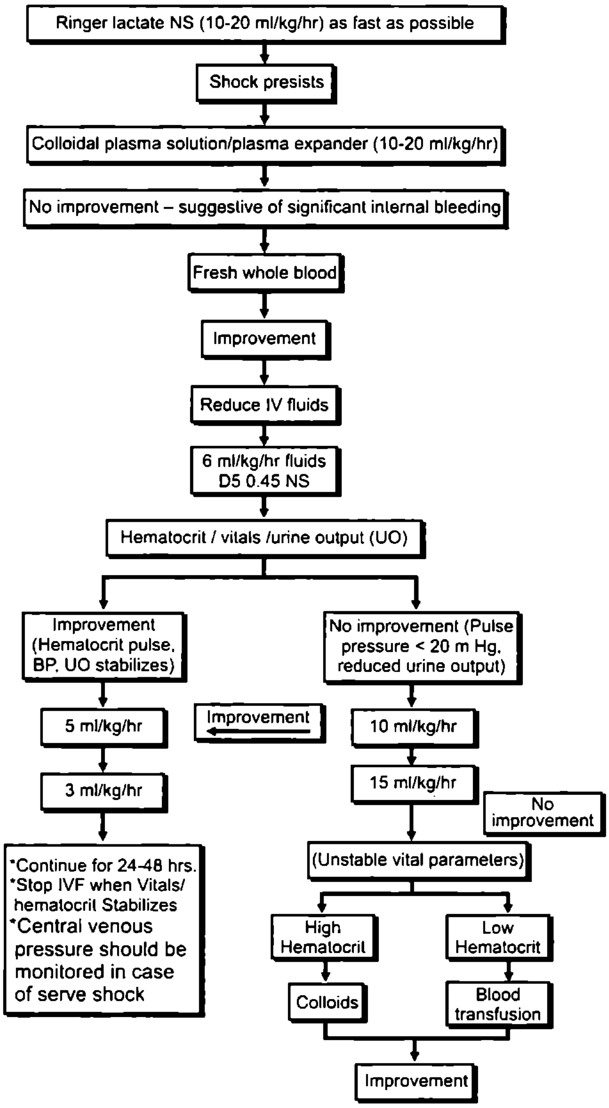
At present no specific drug or vaccine is available against dengue virus. So control primarily is dependent on control of vector.

1. **Environmental changes:** Improving water supply, mosquito proofing of overhead tanks, cisterns and underground reservoirs.
2. **Personal protection:** Protective clothing, mats, coils aerosols (pyrethrum), repellents e.g., Neem oil, DEET, permethrin impregnated in cloth, insecticide treated mosquito nets and curtains.
3. **Biological control:** by Fish-larvivorus fish: Gambria affinis and Peorilia reticulata Bacteria—Bacillus thuringiensis H-14, Bacillus sphaericus—breeds in polluted water.
4. **Chemical control:**
   - 1% temephos sand granules .
   - Space sprays – malathion, fenitrothion, pirimiphos (only in major DHF epidemics).
   - Insect growth regulators – interfere with development of the immature stages of the mosquito in larvae or disruption of pupal stage.

Dengue Vaccine

A tetravalent live attenuated DEN vaccine trial has been done in Thailand. After 3rd dose 89% of subjects seroconverted. Trial suggested that this vaccine has moderate but improvable reactogenicity and high seroconversion rates against 4 serotypes of DEN virus after 3rd dose. A recombinant DEN virus tetravalent vaccine have been developed, which was found to be 92% efficacious in monkeys against all 4 DEN virus serotypes (CHIMERI VAX-DEN).

Flow chart 53.2: Volume replacement protocol in dengue shock syndrome


Ringer lactate NS (10-20 ml/kg/hr) as fast as possible
Shock presists
Colloidal plasma solution/plasma expander (10-20 ml/kg/hr)
No improvement – suggestive of significant internal bleeding
Fresh whole blood
Improvement
Reduce IV fluids
6 ml/kg/hr fluids D5 0.45 NS
Hematocrit / vitals /urine output (UO)
Improvement (Hematocrit pulse, BP, UO stabilizes)
No improvement (Pulse pressure < 20 m Hg, reduced urine output)
5 ml/kg/hr
Improvement
10 ml/kg/hr
3 ml/kg/hr
15 ml/kg/hr
No improvement
•Continue for 24-48 hrs.
•Stop IVF when Vitals/ hematocrit Stabilizes
•Central venous pressure should be monitored in case of serve shock
(Unstable vital parameters)
High Hematocrit
Low Hematocrit
Colloids
Blood transfusion
Improvement

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CHAPTER

Role of Echocardiography in the Pediatric Intensive Care Unit

S Radhakrishnan, V Mahajan

Cardiac surgeons were reluctant to operate an infant with congenital heart disease without cardiac catheterization. Nowadays indications for cardiac catheterization are specific and limited to interventional procedures, or determination of cardiac chamber, pressures, saturations in patients with complex congenital cardiac anatomical and vascular malformations. Cardiac catheterization has been largely replaced by noninvasive cardiac ultrasonography known as echocardiography.

Echocardiography is an important diagnostic tool for diagnosis of congenital heart disease, pericardial disease (fluid, tamponade) and assessment of cardiac function relating to contractility (postsurgery/bypass, septic shock, myocarditis, cardiomyopathy, postcardiac arrest situation), valvular function and to rule out vegetation or other intracardiac lesions.

Echocardiography plays an important role in assessing the patient after surgical correction of congenital heart defects and is vital for success of any pediatric cardiac surgical program. It is a simple noninvasive diagnostic tool which reveals, important information regarding the adequacy of surgical repair, presence of any residual defects, assessment of cardiac function and guiding in the medical and ventilatory therapy of the postsurgical patient. Both transthoracic and transesophageal echocardiography can be done in the postoperative patient but in pediatric age group the use of transesophageal echocardiography is limited to cases when transthoracic echocardiography is not able to provide us with the desired information depending on clinical condition as well as the structures which need to be visualized. The echocardiographer performing the echocardiography should be well versed with normal cardiac anatomy, type of surgery, postoperative care and should have good communication with pediatric cardiac surgeon. This chapter will concentrate on the use of echocardiography in the pediatric intensive care unit.

Indications of Echocardiography

The indications of echocardiography in the postcardiac surgery patient in the PICU are:

a. Low cardiac output state
b. Failure to extubate
c. Hypoxia
d. Physical examination not explained by postoperative physiology
e. Specific surgical concerns
f. Assessment of physiological parameters
g. Miscellaneous

Low cardiac output state

1. Postoperative residual lesions.
2. Hypovolemia
3. Reduced ventricular function
4. Pericardial collection of blood or fluid

Failure to extubate

1. Diaphragmatic paralysis
2. Large pleural collection of blood or fluid

Hypoxia

1. Blocked BT (Blalock Taussig) shunt
2. Tight PA (Pulmonary artery) band and
3. Pulmonary venous obstruction

Physical examination not explained by postoperative physiology

1. Loud murmur after ventricular septal defect (VSD)/tetrology of Fallot (TOF) repair
2. Soft murmur after pulmonary arterial band-? Loose band
3. Pulse discrepancy after patient ductus arteriosus (PDA) ligation–residual coarctation
4. Apical pansystolic murmur after common atrioventricular canal (CAVC) repair–residual mitral regurgitation

Specific surgical concerns Echocardiography is done in the PICU to evaluate the following:

1. Assessment of cardiac patch
2. Evaluation of systemic to pulmonary artery shunt
3. Assessment of pulmonary artery band
4. Assessment of conduit
5. Prosthetic valve function

Assessment of physiological parameters

1. Estimate of pulmonary artery (PA) pressures
2. Assessment of cardiac function
3. Diastolic dysfunction
4. Degree of atrioventricular (AV) valve regurgitation

Miscellaneous

1. Pericardial effusion
2. Pleural effusion
3. Diaphragmatic movements

Assessment of Cardiac Patches

Cardiac patches are used in congenital heart defects to close atrial septal defects, viz ASD, VSD, reconstruct outflow tract, viz right ventricular outflow tract (RVOT) patch, left ventricular outflow tract (LVOT) repair, coarctation repair. The types of patches used include the pericardial patches, Dacron or Gene Tex patches.

Echocardiography of patient with septal defect is used to assess the position of the patch, presence of any residual shunt, any suggestion of foreign body/ growth on the patch. Earlier, contrast echocardiography was widely used to detect residual shunt but after the introduction of color echocardiography the use of contrast echocardiography is limited only to detect shunt across fenestrated Fontan's procedure and baffle leaks. Temporary residual shunt is a common feature, but echocardiography can give a fair idea about the amount of shunt and also to surgically follow such shunts as they disappear. Echocardiography in patient who have undergone the RVOT patch repair is important to assess the degree of regurgitation, any degree of narrowing, assess the outflow patches and any vegetation, attached to patch. Degrees of pulmonary regurgitation is associated with problems encountered in the immediate postoperative period. Assessment of right ventricular function is also very important. The problem with synthetic patch is because of shadowing and reflective nature of these prosthetic materials, which can make the assessment difficult at times.

Evaluation of Systemic to Pulmonary Artery Shunt

Systemic to pulmonary artery shunt is a common palliative operation of patients with decreased pulmonary blood flow or those with right ventricle to pulmonary artery discontinuity. Waterson and Pott's shunt are difficult to visualize as these are interposed between the aorta and pulmonary artery. Blalock Taussing (BT) shunt on the other hand is present some distance away from both aorta and pulmo-nary artery and has considerably more length than other shunts and hence, it can be profiled adequately in the suprasternal views. The right BT shunt can be visualized in the suprasternal long axis view.

Echocardiography can be especially helpful in post- shunt patients who maintain low saturation or those in whom the shunt murmur is faint or not heard, in order to diagnosing any blockage of shunt and plan appropriate management strategy. It can provide gradient across the aorta and pulmonary artery and hence, help estimating the pulmonary artery pressure. Color Doppler is especially useful in revealing the flow across the shunt or detecting any blockage or narrowing of shunt. This however can be demanding especially because the whole length of shunt is not viewed in single view.

Assessment of Pulmonary Artery Band

Echocardiography in patients after pulmonary artery band is usually required in condition where it is suspected either the band is too loose or too tight. This is suspected by increasing pulmonary viscularity and high saturation when the band is loose and decreasing pulmonary vascularity and low or saturation indicating unduly tight pulmonary artery band.

The portion of band can be best evaluated from para-sternal, subcostal and suprasternal views. Doppler echocardiography can be used in record the gradient across the pulmonary artery band in order to estimate the pulmonary artery (PA) pressure. The reported literature indicates that estimated PA pressure on doppler correlates quite well with gradient measurement at cardiac catheterization. The gradients across PA band in the immediate postoperative period can help in fine tuning the medication and ventilatory settings which alter the pulmonary and the systemic resistance.

Assessment of Conduits

In infants and children with congenital heart defects both valved and nonvalved conduits are widely used for the repair of defects, viz. Truncus arteriosus, Pulmonary atresia, etc. The role of echocardiography in the immediate postoperative periods is focussed on detecting any narrowing of the conduit and information regarding the function of the valve. This can be ascertained on two-dimensional echocardiography, color doppler which is visualised as the part when the turbulence starts and pressure gradients across the conduits which give an estimate systemic pressure of the systemic ventricle. Transesophageal echocardiography can help in deleting any rent in the conduit causing any leak across it.

Assessment of Prosthetic Valve Function

Prosthetic heart valves are not commonly used in pediatric age group, but when used can be either mechanical or can be partially or completely made of biological material. Echocardiography evaluation of these kind of valves is difficult because of presence of bright echoes produced by metallic valve.

The parameters to be looked for in the immediate post-operative period include:

a. Position of valve
b. Gradient across the valve
c. Degree of regurgitation
d. Ventricular function
e. Presence of any paravalvular leak

The limitation of transthoracic echocardiography is overcome by use of transesophageal echocardiography especially the posteriorly placed surface of valve. Transesophageal echocardiography has higher sensitivity detect prosthetic valve abnormalities (87% vs 65%) compared to transthoracic echocardiography.

Medical Indications of Echocardiography in PICU

Echocardiography is used in pediatric patients with clinical features of poor cardiac function (low ejection fraction) such as septic shock, myocarditis, ischemic cardiomyopathy, as well as chronic congestive heart failure due to septal defects or valvular abnormalities. Pericardial fluid and tamponae can also be assessed.

SUMMARY

In the PICU patients with cardiogenic shock, septic shock, myocarditis, cardiomyopathy, vegetations, intracardiac lesions, pericarditis/effusion, pericardial tamponade, echocardiography is a vital modality. In a postoperative cardiac intensive care unit, echocardiography (with an experienced pediatric echocardiographer) is essential to assess the adequacy of surgical repair, presence of any residual defects, assessment of cardiac function and guiding in the medical and ventilatory therapy of the post-surgical patient.

CHAPTER

Cardiac Failure

Girish HC, Amit Varma, Praveen Khilnani

DEFINITION

Heart (or cardiac) failure is the pathophysiological state in which the heart is unable to pump blood at a rate commensurate with the requirements of the metabolizing tissues or can do so only from an elevated filling pressure. Term congestive heart failure (CHF) and congestive cardiac failure (CCF) are commonly used to describe cardiac failure.

Cardiac failure should be distinguished from circulatory failure, in which an abnormality of some component of the circulation—the heart, the blood volume, the concentration of oxygenated hemoglobin in the arterial blood, or the vascular bed—is responsible for the inadequate cardiac output.

PROCESSES CAUSING CARDIAC FAILURE

1. *Ventricular volume overload: Increased pulmonary blood flow with no cyanosis* Ventricular septal defect, atrioventricular septal defect, (large) patent ductus arteriosus and renal failure.
2. *Ventricular volume overload: Cyanotic heart disease with increased pulmonary blood flow* Transposition of the great arteries with intact ventricular septum or ventricular septal defect, truncus arteriosus, totally anomalous pulmonary venous return, and some forms of tricuspid atresia.
3. *Ventricular outflow obstruction: Obstructive lesions* Obstructive lesions include critical or severe aortic, mitral, or pulmonary valve stenosis; coarctation of the aorta; hypoplastic left heart syndrome; interrupted aortic arch; totally anomalous pulmonary venous return (TAPVR) with obstruction; and pathologic elevations in pulmonary or systemic vascular resistance.
4. *Myocardial dysfunction:* Myocarditis, postcardiotomy (postcardiopulmonary bypass), sepsis, and drug induced.
5. *Myocardial ischemia:* Coronary anomalies anomalous origin of the left coronary artery from the pulmonary artery and coronary-cameral fistula are examples of coronary anomalies.
6. *Ventricular inflow restriction:* Severe mitral valve stenosis.
7. *High output states:* Anemia, systemic hypermetabolism.
8. *Dysrhythmias:* Tachy or bradydysrhythmias.
9. *Hypoxia*
10. *Miscellaneous lesions:* Myocardial dysfunction syndrome of the newborn, mitral or tricuspid valve regurgitation, vein of Galen or hepatic arteriovenous malformations (AVMs), and hypertrophic cardiomyopathy all can cause congestive heart failure (CHF).

CLINICAL PRESENTATION

The clinical presentation depends in large part on the cause of the CHF and the age of the patient.

Newborns

In newborn infants, CHF interferes with the ability to breathe and feed; crying, stooling, and sleeping may also be affected. Poor perfusion is a hallmark of CHF, manifested by pale, sallow, cyanotic or gray complexion, and poor capillary refill. Feeding may be labored or impossible because of rapid breathing. These patients may sweat profusely.

Physical examination begins with vital signs, with close attention paid to respiratory rate. The heart rate, together with any rhythm irregularities should be noted. Tachycardia may be a cause or an effect of CHF; primary tachycardias must be considered if the heart rate is high and constant.

Four-limb blood pressures should be taken. Aortic obstructive lesions may present in the newborn period and lead to differential blood pressures. If the coarctation of the aorta or any aortic obstructive lesion is in question, then careful palpation of the pulses must be performed.

The temperature and capillary refill of the feet should be tested by the examiner's feel; warm, pink feet with brisk refill are the standard against which these need to be judged. Peripheral cyanosis may be a clue to poor perfusion and CHF. Central cyanosis may be an important sign of CHF because of cyanotic congenital heart disease (CHD). For instance, patients with transposition of the great arteries with intact ventricular septum and obstructed totally anomalous pulmonary venous return (below the diaphragm) present with severe cyanosis early after birth.

A diastolic rumble or gallop occurs in many types of heart failure, especially those with pulmonary over-circulation. Auscultation of the cranium and abdomen may disclose a continuous murmur or bruit, suggesting a vein of Galen (arteriovenous malformation) AVM or hepatic or other abdominal AVM.

Infants

Just as neonates do, infants with CHF often present with poor feeding, lethargy, tachypnea, or diaphoresis. Ductal-dependent lesions are less likely to evidence themselves after the neonatal period, but occasional patients may have coarctation or other disease and late ductal closure. Congenital cardiac malformations that present in later infancy are certain forms of TAPVR and anomalous left coronary artery from the pulmonary artery. Unobstructed forms of TAPVR rely on the patent foramen ovale for flow to the left atrium and the body. The patent foramen ovale may become relatively or even absolutely smaller over the first few months of life, restricting systemic output. This, in combination with the torrential pulmonary blood flow, causes CHF. The anomalous left coronary artery that arises from the pulmonary artery depends on the initial high pulmonary vascular pressure and resistance for coronary bed perfusion. As the pulmonary artery pressure and resistance decrease in the neonate, the myocardium becomes dependent on collateral circulation. This leads to subendocardial and papillary muscle ischemia, with resultant myocardial infarction and mitral valve regurgitation. Infants may be irritable due to chest pain. Thus, the heart has decreased muscle function (both systolic and diastolic) and a volume load from the regurgitant mitral valve. Profound CHF ensues. This lesion, which may be successfully treated surgically, must be differentiated from idiopathic or viral cardiomyopathy, for which no specific treatment is available.

Children and Young Adults

Older children, adolescents, and young adults present with, exercise intolerance, a hallmark of CHF. Abdominal pain or distension may be a result of CHF. Tachypnea, dyspnea on exertion, and shortness of breath may be present. Examination might show some of the features just listed, and ascites and peripheral edema, which are less common in younger children, may be present. Rales are uncommon in this age group.

Heart failure may be a result of systolic or diastolic Dysfunction (Table 55.1).

A lot of importance is given to ejection fraction and shortening fraction which are indices of systolic function.The importance of abnormalities of diastolic function in the pathogenesis of heart failure is being increasingly appreciated. There can be significant diastolic dysfunction of the heart with normal indices of systolic function. There should be proper evaluation of the diastolic dysfunction which can be assessed by the pattern of ventricular filling. The detailed discussion of this is beyond the scope of this chapter. Readers are referred to the cardiology textbooks for this.

Radiographic Findings

Although the standard posteroanterior and lateral chest radiograph provides limited information about chamber size, the presence of overall cardiomegaly (a cardiothoracic ratio above 0.50) is a strong

Table 55.1: Various causes of heart failure

- I. *Impaired Systolic (Contractile) Function*
  - A. Ischemic damage or dysfunction
    - 1. Myocardial infarction
    - 2. Persistent or intermittent myocardial ischemia
    - 3. Hypoperfusion (shock)
  - B. Chronic pressure overloading
    - 1. Hypertension
    - 2. Obstructive valvular disease
  - C. Chronic volume overload
    - 1. Regurgitant valvular disease
    - 2. Intracardiac left-to-right shunting
    - 3. Extracardiac shunting
  - D. Non-ischemic dilated cardiomyopathy
    - 1. Familial/genetic disorders
    - 2. Toxic/drug-induced damage
    - 3. Immunologically mediated necrosis
    - 4. Infectious agents
    - 5. Metabolic disorders
    - 6. Infiltrative processes
    - 7. Idiopathic conditions
- II. *Impaired Diastolic Function (Restricted Filling, Increased Stiffness)*
  - A. Pathologic myocardial hypertrophy
    - 1. Primary (hypertrophic cardiomyopathies)
    - 2. Secondary (hypertension)
  - B. Aging
  - C. Ischemic fibrosis
  - D. Restrictive cardiomyopathy
    - 1. Infiltrative disorders (amyloidosis, sarcoidosis)
    - 2. Storage diseases (hemochromatosis, genetic abnormalities)
  - E. Endomyocardial disorders

indicator of heart failure or another cause of cardiomegaly (especially valvular insufficiency). However, nearly 50% of heart failure patients do not have this high a cardiothoracic ratio.

Most patients with acute heart failure, but only a minority of those with chronic heart failure, will have evidence of pulmonary venous hypertension (upper lobe redistribution, enlarged pulmonary veins) or interstitial (haziness of the central vascular shadows or increased central interstitial lung markings) or pulmonary (perihilar or patchy peripheral infiltrates) edema. The absence of these findings reflects both the subjectivity of interpretation and the increased capacity of the lymphatics to remove interstitial and alveolar fluid in chronic heart failure. This absence of radiographic findings is consistent with the absence of rales in most patients with chronic heart failure despite markedly elevated pulmonary venous pressures. Pleural effusions are important adjunctive evidence of heart failure. Characteristically, these are more common and larger on the right side than left side, reflecting the greater pleural surface area of the right lung.

THE ELECTROCARDIOGRAM

The major importance of the electrocardiogram is to evaluate cardiac rhythm and detect evidence of chamber enlargement.

Echocardiography

(See Chapter on Pediatric Echocardiography)

Echocardiography provides a quantitative assessment of left ventricular function, which can, in the presence of appropriate symptoms and signs, confirm the presence of heart failure due to systolic dysfunction or indicate whether the patient has heart failure with preserved systolic function. The echocardiogram also provides a wealth of additional valuable information, including assessment of left and right ventricular size, evaluation of the heart valves, and diagnosis of left ventricular hypertrophy.

The echocardiogram has generally replaced the chest radiograph in the diagnostic assessment of heart failure.

Management

Management of a child with cardiac failure will depend upon the etiology and according some or all of the following measures will apply:

In acute heartfailure, priorities as in the management of cardiogenic shock need to be followed. Admission to the PICU, oxygen administration, airway control and mechanical ventilation are important supportive components in a decompensating child with cardiogenic shock.

Acute inotropic support of the failing heart with sympathomimetics and phosphodiesterase inhibitors such as milrinone have been discussed in length elsewhere in this book. So this discussion will be limited to current standing on the chronic management of congestive heart failure in infants and children.

FLUID MANAGEMENT

In a given patient with a given cardiac pathology and state of the myocardium, there is an optimal filling pressure to sustain a good cardiac output. Vigorous diuresis may be detrimental particularly in a patient with predominantly diastolic dysfunction as they usually require high filling pressures for ventricular filling. At the same time excessive fluid loading in a failing heart may cause pulmonary and systemic edema thus diminishing oxygen supply. Hence optimal fluid management is a cornerstone in the therapy of congestive heart failure.

DIGOXIN

Digoxin may have several beneficial effects in patients with chronic heart failure. In addition to its inotropic effects through Na^+/K^+ ATPase inhibition, digoxin may also have peripheral effects that attenuate the actions of the neurohormonal system. Several studies have shown that digoxin improves symptoms in adults with heart failure.[1,2] However, no studies with digoxin in chronic heart failure have yet shown survival improvement. Although digoxin is widely used to treat heart failure in children, few data support or refute its use. Although some studies found benefit from digoxin in these patients, others failed to do so.[3,4] Virtually no data are available on the use of digoxin in children with heart failure caused by systemic ventricular systolic dysfunction.

MODULATORS OF RENIN-ANGIOTENSIN-ALDOSTERONE AXES

The role of Renin-Angiotensin and Renin-Aldosterone axes in the pathophysiology of congestive cardiac failure has been well established for many years . But the role of these hormones in the adverse vascular remodeling in the heart is only recently elucidated. Indeed, each effector hormone of the renin–angiotensin–aldosterone system contributes independently to adverse vascular remodeling:

ACE Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors inhibit the enzyme responsible for the conversion of angiotensin I to angiotensin II. Angiotensin converting enzyme inhibitors have effects on both th peripheral vascular and neurohormonal systems i addition to direct effects on the myocardium. At th time, angiotensin-converting enzyme inhibitors ar thought to exert favorable effects on cardia remodeling. Four major studies in more than 7,00 adults with heart failure have shown improved survival with the use of angiotensin-convertin enzyme inhibitors. These include the Captopril Digoxin Multi-center Trial, Studies of Left Ventricula Dysfunction (SOLVD), Vasodilator Heart Failure Trial (V-HeFT), and The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS).[5-8] In addition to their beneficial effects on survival angiotensin-converting enzyme inhibitors have also improved symptoms in adults with heart failure. Mos studies have also shown that higher doses o angiotensin-converting enzyme inhibitors are better than lower doses for improving survival and symptoms.[9,10]

The role of angiotensin-converting enzyme inhibitors in the treatment of heart failure in children is much less clear. Angiotensin-converting enzyme inhibitors may have acute hemodynamic benefits in children with heart failure caused by large left-to-right shunts[11-15] and may also benefit children whose heart failure is caused by systemic ventricular systolic dysfunction.[16,17] However, the only randomized placebo-controlled trial of angiotensin-converting enzyme inhibitors in children with heart disease was in children with single ventricle physiology who had undergone the Fontan procedure.[18]

Aldosterone Antagonists

Aldosterone's contribution to the retention of sodium in patients with congestive heart failure and also in the pathophysiology of cirrhosis, and the nephrotic syndrome has been well established.[19-22] In heart failure, there is presence of increased amounts of aldosterone in urine and plasma and this correlates with the retention of sodium and water. Morphologic studies indicate that a chronic excess of mineralocorticoid (plus salt loading) can cause fibrosis in the atria and ventricles as well as the kidneys and other organs in humans and animals.[23,24] Thus, aldosterone may promote the remodeling of organs and fibrosis. In rats with uninephrectomy and are given aldosterone and salt, spiranolactone prevents cardiac fibrosis even when it is given in doses that do not prevent hypertension or left ventricular hypertrophy.

In an international study (the Randomized Aldactone Evaluation Study [RALES]), conducted in 19 countries on 5 continents and involving more than 1660 patients with moderately severe or severe congestive heart failure, there was a 30 percent reduction in the rate of death from any cause among patients treated with spironolactone (25 mg daily) in combination with an ACE inhibitor and a loop diuretic, as compared with patients who received placebo. In addition, there were similar reductions in sudden death from cardiac causes, death from progressive cardiac failure, and hospitalizations related to symptomatic heart failure.

Beta Blockers

β-adrenergic receptor (β-AR) agonists improve myocardial contractility acutely. However, long-term stimulation of the β-adrenergic system in chronic heart failure appears to be associated with a worse outcome, potentially caused by a feedback mechanism whereby increased β-AR stimulation leads to desensitization.[25] In patients with chronic congestive heart failure, in whom an increase in β-AR stimulation from increased sympathetic nervous system activity leads to down-regulation and decreased sensitivity of β-AR along with progressive myocardial dysfunction.[26] The use of β-AR blocking agents may therefore paradoxically maintain β-AR sensitivity and improve myocardial function.

Waagstein[27] first reported the use of beta blockers in a small group of adults with heart failure in 1975. Since that time, an enormous amount of research has gone into the development and subsequent analysis of numerous beta blockers to determine their safety and efficacy in treating heart failure in adults.

It was not until 1996 that two studies finally showed a survival benefit from the use of beta blockers in adults with chronic heart failure. In the Multicenter Oral Carvedilol Heart Failure Assessment (MOCHA) trial, Bristow and colleagues[28] randomized 345 adults with ischemic or nonischemic cardiomyopathy to receive either placebo or carvedilol (12.5-50 mg daily). Carvedilol had no benefit on the primary end point, submaximal exercise. However, a dose-dependent reduction in both mortality and hospitalization was statistically significant. Mortality decreased from 14.3 percent in the placebo group to 4.8 percent in those who received carvedilol 12.5 mg daily, to 3.4 percent in those who received carvedilol 25 mg daily, to 1.1 percent in those who received carvedilol 50 mg daily. A similar dose-dependent increase was seen in left ventricular ejection fraction. Packer and colleagues[29] randomized 1,094 adults with mild to moderate heart failure to placebo or carvedilol; they found a 65 percent reduction in mortality in those who received carvedilol and a 27 percent reduction in the risk of hospitalization for cardiovascular causes.

Until recently, beta-blockers were recommended only for the treatment of mild to moderate heart failure in adults. However, the recent Carvedilol Prospective Randomized Cumulative Survival Trial (COPERNICUS) found a 35 percent reduction in all-cause mortality in adults with severe (NYHA class IV) heart failure symptoms who had received carvedilol (volume over-loaded patients were excluded from the study).[29]

Although the mechanism of action of beta-blockers in heart failure is still being defined, a large body of basic and clinical investigation indicates that their major benefit is prevention or reversal of the myocardial dysfunction that occurs because of sympathetic activation, primarily from norepinephrine. The adverse effects of sympathetic activation include increased ventricular volumes and pressures caused by peripheral vasoconstriction, cardiac hypertrophy and coronary vasoconstriction leading to ischemia, increased programmed cell death, and increased risk of arrhythmias.

Other proposed beneficial effects of beta-blockers are their negative chronotropic effects, up-regulation of beta-receptors (although many beta-blockers do not up-regulate beta-receptors), coronary vasodilatory effects, and possibly antioxidant effects in beta-blockers such as carvedilol.

Differences between beta-blockers used in heart failure are primarily related to their β_1 or β_2 receptor selectivity and ancillary properties. First-generation beta blockers are nonselective, e.g., propranolol; second generation beta-blockers are selective for b1 without ancillary properties e.g., metoprolol, and third generation beta blockers have ancillary properties (carvedilol, bucindolol).

Existing knowledge about the effects of beta-blockers in children with heart failure is entirely anecdotal. There are reports of the efficacy of metoprolol in teens with anthracycline-induced cardiomyopathy,[30] in children awaiting heart transplantation,[31] and in children with congenital heart disease and dilated cardiomyopathy.[32] A multicenter retrospective report of carvedilol in children has also suggested a potential benefit in improved ventricular performance and symptoms.[33] However, as of yet no prospective randomized trials of β-blockers in children have been completed that could clearly define safety and efficacy; studies are underway.

As far as salt restriction in heart failure is concerned, there is still a controversy. Given the importance of sodium as a necessary modulator of aldosterone-associated vascular remodeling, it could be argued that dietary sodium restriction should be severe. On the other hand, severe sodium restriction together with diuretic treatment can lead to volume contraction and further activation of the renin–angiotensin–aldosterone system. Hence, the optimal level of daily sodium in patients with congestive heart failure is uncertain.

CONCLUSION

Acute treatment of congestive heart failure includes judicious fluid management (with optimal use of fluids and diuretics), inotropic support including sympathomimetics and phosphodiesterase inhibitors like milrinone, minimizing oxygen requirements with mechanical ventilation and mechanical support of the heart with ventricular assist devices and ECMO. Of course, it also should include correcting the cause of heart failure surgically if amenable such as critical aortic stenosis, pericardial effusion. Heart transplantation has a definite place in treatment of end stage heart disease (such as ischemic cardiomyopathy, endomyocardial fibroelastosis) and is discussed elsewhere.

Chronic treatment of heart failure should include a small dose of an aldosterone-receptor antagonist, given in combination with an ACE inhibitor and a loop diuretic, with or without digoxin. Serum potassium and creatinine should be measured after such combination therapy is initiated and on a regular basis thereafter. Supplemental potassium, used to offset the kaliuresis, associated with loop diuretics, should be discontinued when therapy with drugs that decrease aldosterone secretion or action is begun.

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CHAPTER

Cardiac Dysrhythmias in Pediatric Intensive Care

Mary L Falterman, Praveen Khilnani

Cardiac rhythm disturbances frequently occur in those infants and children requiring intensive care. These dysrhythmias may occur in patients with structural/acquired heart disease, after repair of congenital heart defect or may accompany a non-cardiac systemic illness. This article will discuss some of the more commonly occurring dysrhythmias, their etiologies and how to acutely treat them. Following a brief discussion of normal sinus rhythm (NSR), the four major electrophysiologic classes will be reviewed (bradycardia and escape rhythms, premature beats, tachydysrhythmias and dysrhythmias that result from atrioventricular block). Finally, in summary, a commonsense approach to management of common cardiac dysrhythmias will be discussed.

Physiology

The Sinu-atrial (SA) node, located in the high right atrium, is the usual pacemaker of the heart since these cells have the highest rate of spontaneous depolarization. Conduc-tion then occurs through the atrial tissue down to the atrioventricular (AV) node, along the bundle of His and through the right and left bundle branches to the ventricular myocardium. The average conduction time through the atrium is 0.20 seconds with the majority of this time within the node; the usual conduction time within the ventricle is 0.08 seconds. In NSR a P wave must precede each QRS complex, and each QRS complex must be preceded by a P wave. The normal P wave axis is between 0 and 90 degrees. The normal range for heart rate is age dependent.

Diagnosis of Dysrhythmias

The infant or child with an underlying dysrhythmia can present in multiple ways. For example, infants with persistent supraventricular tachycardia (SVT) may present in a fashion similar to those with large shunt lesions such as VSD, or myocardial dysfunction as seen with anomalous left coronary artery (ALCAPA). Since the symptoms resulting from a dysrhythmia are caused by an acute or subacute decrease in cardiac output (CO) and hypoperfusion, children may be initially diagnosed as having systemic infection, seizure disorders, hysteria or central nervous system pathology. A thorough history and clinical examination is extremely important. Heart rate too fast to count, throbbing in the chest, poor feeding, lethargy, pale color are common presenting symptoms in supraventricular tachycardia frequently pointed out by the parent. Older children can complain of palpitations, skipbeats, fast pulse rate and so on.

A 12 lead ECG with a 2-3 minute rhythm strip should be obtained on any child with a suspected rate, or rhythm disturbance. Many times the first indication of an underlying dysrhythmia is on routine ECG or during monitoring in the PICU (Pediatric intensive care unit) setting. In addition a basic electrolyte panel to include sodium, potassium, calcium, magnesium should be obtained. Other investigations such as chest X-ray and echocardiography can be guided by further clinical examination.

Bradycardia and Escape Rhythms

Bradycardia implies an abnormally low sinus rate. Normal values have been based on 24 hour holter recordings (best rate counted over 60 seconds), 60/minute for a sleeping infant and children up to six years, 45/minute for a child 7 to 11 years, and 40/minute for a teenager.[1,2]

Bradycardia, a frequent finding in the PICU, may result from increased vagal tone associated with pharyngeal stimulation following nasogastric or endotracheal tube suctioning. Other causes include elevated intracranial pressure, central nervous system injury, abdominal distension, hypothyroidism and metabolic abnormalities such as hypoglycemia, hypothermia, hypoxia, acidosis or hypercalcemia. Drugs, both in toxic dose, e.g., digoxin, quinidine and the organophosphates, or in therapeutic doses e.g., propranolol, verapamil and halothane may be contributing factors. Jervel-Lange-Nielsen and Romano-Ward, both syndromes with long QT interval may present as sinus bradycardia.[3,4]

Escape rhythms may occur during episodes of bradycardia if the sinus node is suppressed (commonly from vagal stimulation) as subsidiary pacemakers take over and the tissue with the next highest "automaticity" rate fires. (The SA node is faster than the atrium, which is faster than the AV node, which is faster than the ventricle.) Normally subsidiary pacemakers in atria, AV junction and ventricular Purkinje system are suppressed by the inherently faster automaticity rate of the SA node. Two or more escape beats in a row constitutes an escape rhythm. Acute causes of an escape rhythm are the same as those for REM (Rapid eye movement) sleep when vagal tone is high. Chronically escape rhythms can occur following atrial operations, e.g. Mustard procedure.

Many children who are in NSR may have heart rates that vary, but yet remain within the normal range over a several minute rhythm strip. This variation in P-P-P interval followed by a normal QRS is a sinus dysrhythmia and is simply due to cyclical respiratory suppression of the more rapidly firing cells in the SA node with slightly slower pace maker cells then taking over. With normal rates, this should be considered a variant of normal.

Those "slow" rhythms that cause hemodynamic instability should be treated initially either with atropine or epinephrine. Epinephrine (0.01 mg/kg) is recom-mended for the infant, while atropine in vagolytic doses (0.02 mg/kg) is the first line of treatment for children. If necessary, infusions of epinephrine or isoproterenol (0.1-1.0 u/k/min) can then be titrated to obtain stability. In cases of sinus node dysfunction, cardiac pacing may be required.[5]

Premature Beats[6,7]

Premature beats may originate from the atria, AV junction or ventricle. In normal sinus rhythm (NSR), a P wave that occurs more than 0.08 seconds before the next expected P wave is considered premature resulting in a premature atrial contraction (PAC). This PAC may be conducted normally (with normal QRS configuration), aberrantly (with wide QRS complex) or may be blocked and not conducted to the ventricles at all. Acutely these may be caused by mechanical irritation from central venous lines, metabolic abnormalities (hypokalemia, hypercalcemia, hypoxia, hypoglycemia or drugs, e.g. digoxin, imipramine and sympathomimetics. A premature ventricular contraction (PVC) similarly occurs before the next expected QRS in a regular rhythm, however, the morphology of the QRS complex is nearly always different from the regular QRS, the complex is prolonged with STT wave changes, and with a T wave opposite in direction to that of the QRS complex. There is no premature P wave preceding the premature QRS. Fusion beats in which depolarization begins at 2 sites in the ventricle with resulting "fusion" of both morphologies on surface ECG confirms the ventricular origin. It is important to identify both QRS complexes elsewhere on the strip and that the "fusion" beat has characteristic of both.

Isolated, uniform PVCs that occur < 10/minute and in a patient with a structurally normal heart are common and are usually considered benign.[7] Even cases of trigeminy (every third beat is abnormal) or bigeminy are not uncommon, and with hemodynamic stability, do not need urgent treatment. PVCs in couplets or with varying morphologies need immediate evaluation since these rhythms may deteriorate into ventricular tachycardia (see tachydysrhythmias).

Causes of acute onset of PVC, are similar to those of PACs (mechanical stimulation from catheters or pacing wires, hypoxia or electrolyte abnormalities). Chronically, PVCs can accompany structural heart disease (especially post-operatively), ventricular tumors. PVCs may be treated with lidocaine intravenously in dosage of 1 mg/kg. Primary cause of PVCs must be corrected.

Tachydysrhythmias

Three categories of commonly seen tachycardias will be discussed:

- Supraventricular tachycardia (SVT)
- Ventricular tachycardia (VT)
- Junctional ectopic tachycardia (JET)

Supraventricular Tachycardia (SVT)

Supraventricular tachycardia is the most common sustained tachydysrhythmia in children. Most commonly in children younger than 12 years of age, the SVT is caused by an accessory atrioventricular connection; in teenage years, atrioventricular node reentry tachycardia is also an important cause of SVT.[8]

In accessory connection-mediated tachycardia, the common tachycardia circuit, i.e. orthodromic tachycardia, is comprised of antegrade conduction down the atrioventricular node and retrograde conduction up the accessory connection. If the accessory connection also has antegrade conduction properties, the term WPW (Wolf Parkinson White syndrome) is applicable. With WPW, the surface ECG shows the characteristic short PR interval, a delta wave and wide QRS complex (Fig. 56.1). Patients with WPW not only can have orthodromic tachycardia but also can have antidromic tachycardia. The circuit of antidromic tachycardia involves antegrade conduction down the accessory connection, with retrograde conduction up the atrioventricular node or alternative accessory connection. WPW patients are also prone to have atrial flutter with rapid conduction down the accessory connection. Tachycardias associated with WPW and that involve antegrade conduction down the accessory connection may be dangerous and associated with sudden cardiac death. The risk for sudden cardiac death in patients with WPW is 1 percent every 10 years. For this reason, any child with WPW and a syncopal tachycardia episode should be considered for a catheter ablation procedure.

The classic ECG characteristic of accessory connection-mediated orthodromic tachycardia is a narrow QRS tachycardia with a retrograde P wave inscribed after the QRS in the ST segment (commonly seen SVT) (Fig. 56.2). Antidromic SVT has a wide QRS morphology and resembles VT (SVT with aberrent conduction). Both antidromic and orthodromic SVT are reentrant in nature, so they can have an abrupt onset and termination.

Treatment of SVT Acute termination of orthodromic SVT can be accomplished by vagal maneuvers such as an ice pack on the face, or with medications. Adenosine (0.1 mg/kg) given intravenous rapidly, breaks the orthodromic circuit at the level of the atrioventricular node. Other intravenous medications, such as digoxin, procainamide, propranolol and amiodarone can also be used to acutely terminate SVT. Intravenous verapamil is contraindicated in infants and small children. It can be used cautiously in older children.

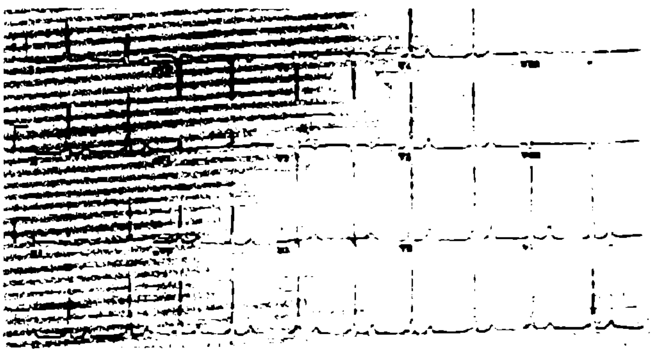


Fig. 56.1: ECG of a patient with Wolff-Parkinson-White. Note the short PR interval, delta complex wave and wide QRS complex

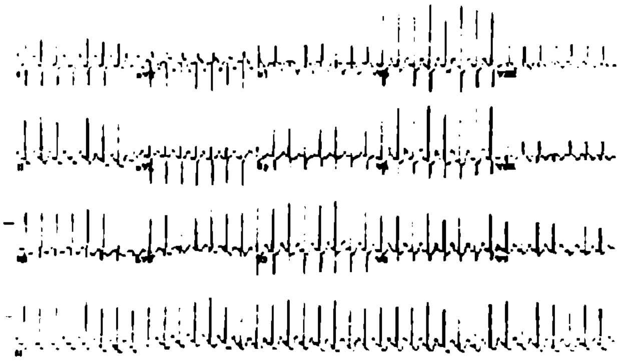


Fig. 56.2: ECG of a child with orthodromic SVT. Note the retrograde P waves in the ST segments

Long-term medical treatment of patients with orthodromic SVT usually involves digoxin or beta-blocker therapy. Other medications, such as flecainaide, procainamide, sotalol, amiodarone and verapamil are used for more recalcitrant SVT. Digoxin should be avoided in children with WPW because of its potential prodysrhythmic effects. It can enhance the conduction properties of the accessory pathway, resulting in a more rapid ventricular rate during atrial flutter and an increased risk for sudden death.

Radiofrequency catheter ablation has become an important treatment of chronic atrioventricular reentrant tachycardia. Success rates for radiofrequency catheter ablation and accessory connections depend on the age of the patient, structures of the heart, pathway location, and operator experience. In general, success rates in experienced centers range between 85 and 95 percent.

Ventricular Tachycardia (VT)

Ventricular tachycardia in children is rare compared with the incidence of SVT. Because of this fact, VT is often misdiagnosed and treated as SVT in children. The wide QRS tachycardia in children should be considered to be ventricular tachycardia until proven otherwise. The "wideness" of the QRS in pediatric VT may be subtle, so vigilance is important. The presence of atrioventricular dissociation during tachycardia is diagnostic of VT.[9]

In children, VT occurs in the context of a normal heart or, more importantly, with structural heart disease. In infants, VT can be associated with hemartomatous growths on the ventricles. These automatic VTs may be responsive to medications but may also necessitate surgical ablation procedures because of hemodynamic compromise. Many VTs of this nature resolve as these children mature.

Ventricular tachycardia can be associated with repaired congenital heart disease (CHD), myocarditis, ALCAPA, mitral valve prolapse (MVP), primary cardiac tumors, cardiomyopathy, drugs (amphetamines) or in the post-operative period. It can lead to hypotension or ventricular fibrillation.

Children with heart lesions, such as repaired tetrology of Fallot, can have VT that presents as sudden cardiac death. Antidysrhythmic medications, surgical or catheter ablation procedures, and defibrillator placement may be needed for control of this variety of VT.

Other types of VT occur in children with normal hearts. One such VT has a left-bundle-branch-block morphology with an inferior axis. This VT is automatic in nature, catecholamine sensitive and originates in the muscle of the right ventricular outflow tract. Another VT seen in children with normal hearts is thought to be secondary to reentry around the Purkinje network of the left posterior fascicle. Treatment regimens for both of these varieties of VT include no intervention, antiarrthymic medications, or ablation procedures.

A "wide" QRS tachycardia can be either ventricular tachycardia (VT), SVT with aberration or atrialflutter with aberration. While SVT with aberration is fairly common in adults it occurs < 10 percent of the time with SVT in children. Atrial flutter with aberration is rare would have varying amounts of aberration.

It should be emphasized that any infant or child with wide QRS tachycardia should be considered to have VT.

Treatment of VT The principles of management are to treat the hypoxia and underlying electrolyte imbalance. Drugs useful are lignocaine (lidocaine) (1.0 mg/kg), amiodarone, propanolol or procainamide. After bolus dose of lidocaine, a drip at 20 to 50 microgram/kg/minute needs to be instituted. Synchronized DC cardioversion (0.5 to 1 joule/kg) is used for pulselers vetricular tachycardia (unstable) followed by amiodarone. Temporary pacing is indicated if SC shock and medications fail.

Junctional Ectopic Tachycardia (JET)

JET is one of the most difficult and challenging dysrhythmias in a postoperative cardiac surgical child. It can be life-threatening and very difficult to control.[10,11] It is more common after the repair of tetrology of Fallot, but can also be seen after repair of ventricular septal defect, AV septal defect, or other complex intracardiac repairs. Although this dysrhythmia usually subsides after 48 to 72 hours after surgery, but untreated it can lead to major morbidity and mortality. Etiology is considered to be secondary to enhanced automaticity of bundle of HIS. AV dissociation is usually present. JET is resistant to drug therapy, DC cardioversion, or overdrive pacing. Digoxin should be administered. Amiodarone has been found to be effective in some cases. Beta blockers are contraindicated. Sympathetic stimulation and inotropic therapy should be minimized as much as feasible, and calcium and potassium should be corrected. Sedative and muscle relaxants should be administered. Cooling to core temperature of 33 to 35 degree centigrade has been found to be helpful to control JET.

Atrioventricular (AV) Block[12,13]

AV block is defined as either a delay in or lack of conduction from atria to ventricle. First degree block occurs when there is prolonged conduction within the atria or AV node. Without other conduction abnormalities, this usually results in a slow but hemodynamically stable rhythm. Mobitz I second degree block is caused by a conduction delay within the AV node resulting in progressive prolongation of the P-R interval until eventually a dropped beat occurs. This also is usually a stable rhythm. Mobitz type II block, in which beats are dropped irregularly is more ominous as it may progress to complete AV block.

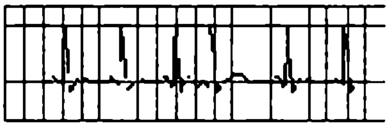
Complete heart block (CHB) is defined as total lack of conduction from the atria to ventricles. The atria and ventricles are both beating independently. Usually the atrial rate is faster with a junctional escape ventricular rhythm. A long rhythm strip may be required to document dissociation as the independent rates can be very similar and simulate NSR.

Complete AV block may be congenital or acquired. Infants of mothers with collagen vascular disease may present at birth with congenital heart block or develop it within the newborn period. CHB is commonly seen in congenital heart disease with ventricular inversion. Acute causes include recent surgery near the node, myocarditis (particularly diphtheria) and anti-dysrhythmic drugs in toxic levels. Treatment is as for the bradydysrhythmia. Pacemaker placement may be necessary for symptomatic or postoperative patients with persistent CHB lasting longer than two weeks postsurgery.[14,15]

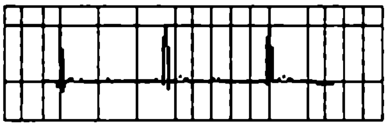
Following are some brief illustrations of common dysrhythmias.

Atrial Arrhythmias

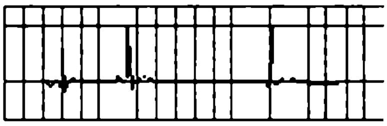
Premature atrial beat: The 4th P wave has a different configuration, indicating a different (non-sinus) origin. It is followed by a post-ectopic pause. This is usually a benign arrhythmia, but can cause problems if the premature atrial beats are early and blocked, thereby, reducing the effective heart rate. This can be a significant problem in infants (See below).



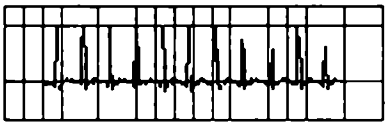
Nodal (junctional) escape beat: The 3rd QRS complex is not preceded by a P wave, but has a nodal (junctional) origin. The atria are depolarized in a retrograde fashion and the corresponding P is masked by the QRS complex. It is usually a benign arrhythmia, which can often be found in patients with long sinus pauses (below).



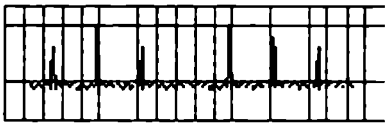
Sinus pause: The expected P wave does not occur (nor, does a junctional escape take place). This is either sinus arrest, or a sinus exit block. This arrhythmia will only cause a problem if the sinus arrest is of long duration and there are no nodal escape beats (below).



Supraventricular tachycardia (SVT): Note the apparent absence of P waves in the face of a narrow QRS tachycardia. Electrophysiological studies would show that the P wave is either within the QRS complex or immediately following the QRS. If sustained, this arrhythmia results in cardiac decompensation. Ventricular filling is affected, resulting in a decrease of cardiac output. This arrhythmia is often seen in infants, who in the majority "out-grow it," but can be associated with Wolff-Parkinson-White Syndrome (below).

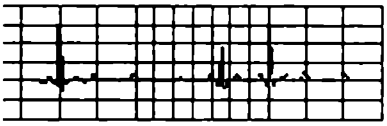


Atrial flutter: Note the rapid "saw-tooth" pattern of the atrial flutter waves and irregular RR intervals. This arrhythmia does not occur in the absence of significant cardiac abnormalities. Depending upon the ventricular capture rate, this can result in cardiac decompensation. In situations where atrial contraction is needed for adequate cardiac performance, this arrhythmia is also a significant problem (below).

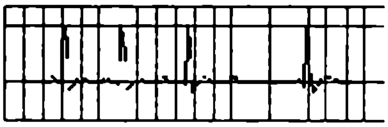


Atrio-Ventricular Block

2° AV Block (Mobitz Type II): Note the non-conduction of every other P wave. This arrhythmia can be a benign occurrence without other heart problems. It can, however, occur in the presence of cardiac abnormalities, and, therefore, this should be ruled-out (below).



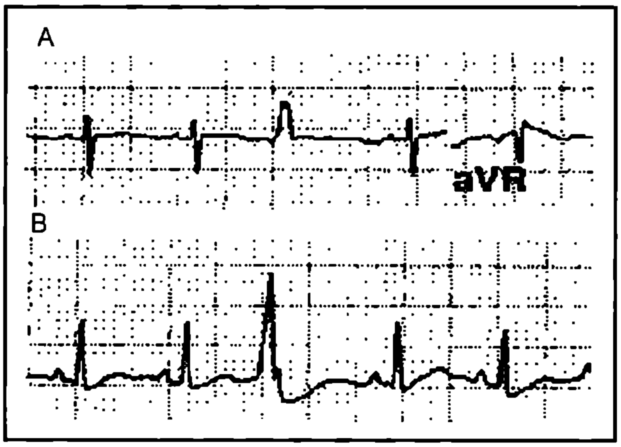
2° AV Block of Wenckebach Type (Mobitz Type I): Beginning with the 2nd P wave, note the increasing PR interval until the last P is no longer conducted and the cycle recurs (below).



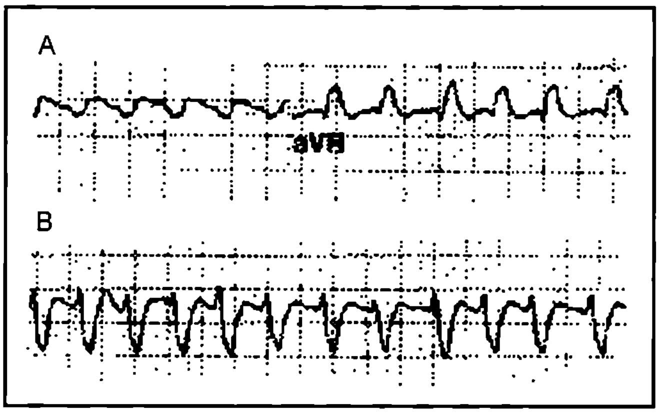
3° AV Block (complete AV Block, complete AV dissociation): P and QRS complexes have no temporal relationship. Atria and ventricles beat independently. If the ventricular rate is appropriate for the patient's age, this arrhythmia is well tolerated. However, a wide QRS complex with a slow rate can result in syncope and possible death. This arrhythmia takes on special significance when related to previous cardiac abnormalities.

Ventricular Ectopic Beats

Single premature ventricular beat with postectopic pause: The PVC is not preceded by a P wave, occurs prematurely, has a wide QRS complex with altered T wave, and blocks the next P wave, thus causing a pause. This is usually a benign arrhythmia, especially if it disappears with exercise.



Ventricular tachycardia Commonly caused by myocarditis, LCAPA, MVP, primary cardiac tumors, cardio-myopathy, drugs (amphetamines) or post-operative. It can lead to hypotension or ventricular fibrillation.



Ventricular fibrillation It is characterized by bizarre ventricular QRS pattern of varying size and configuration. The rate is rapid and irregular and is a life-threatening emergency.

Antidysrhythmic Drugs[16]

After the initial stabilization of the patient with an acute dysrhythmia, comes the question of further management.

This could include:

i. The use of drugs
ii. Catheter or surgical ablation
iii. Placement of antitachycardia devices/ pacemaker or
iv. Observation alone without drug treatment.

Antidysrhythmic drugs are the most commonly used treatment modality. There are a number of classifications, but the most well-known is the Vaughan William (VW) drug classification. This is based on effects on the action potential and duration, and effects on a particular dysrhythmia.

Digoxin is the most frequently used antidysrhythmic in the pediatric population and, interestingly enough, is not included in the original V-W classification. Before introduction of Adenosine, it had been traditionally considered the first line of treatment for symptomatic SVT in the infant and young child. Through stimulation of the autonomic nervous system (ANS), the cells in the atria are hyperpolarized and conduction within the SA and AV node slowed. For those patients with SVT and Wolf-Parkinson-White (WPW) syndrome, digoxin may increase retrograde conduction through the AV node, thus possibly precipitating life-threatening dysrhythmias via conduction, across the accessory pathway.[17] Therefore, in those patients, it may be prudent to use another agent such as a beta adrenergic blocker. There is no role for digoxin in treatment of ventricular dysrhythmias.

The usual loading dose of, digoxin is 30-40 microgram/kg given intravenously in increments over 24 hours. The oral maintenance dose is 10 micrograms/kg/day divided every 12 hours. Since digoxin is renally excreted, those children with kidney disease may require a lower dosing frequency.

Frequent side effects include nausea, vomiting and anorexia. In therapeutic levels, there may be prolongation of P-R interval and shortening of the QRS. With toxicity, multiple types of dysrhythmias may occur including bidirectional ventricular tachycardia. Serum digoxin level, if available should be kept below 2 microgram/ml to avoid toxicity.

Agents such as quinidine (class 1) slow the maximum rate of depolarization, and inhibit the rapid inward sodium current. Quinidine, available only in oral form, can be used to treat both chronic SVT and VT. When used to treat atrial fibrillation/flutter, digoxin must be begun first to block the AV node and prevent 1 : 1 conduction and paroxysmal tachycardia. Use of quinidine in the pediatric population is limited by its multiple and significant side effects. Nausea and vomiting are common; it can worsen congestive heart disease; its prodysrhythmic effects can worsen underlying dysrhythmias. Procainamide has similar properties and is available in both oral and intravenous forms.

The competitive beta adrenergic blocking agents (class II) can be used to treat both supraventricular and ventricular dysrhythmias. Propranolol is commonly added as a second agent to patients with breakthrough SVT already on digoxin. In the older child, propranolol or its long acting counterpart atenolol can be used as the first line drug. Atenolol unlike propranolol does not have membrane stabilizing properties and for this reason it may not be as effective, but it also does not have CNS side effects (depression, nightmares) that propranolol can exhibit.

Adenosine can be used acutely to terminate those SVTs that use the AV node as part of the reentrant circuit.[18] It has an extremely short half-life and should be given as a bolus (0.1 mg per kg). Side effects are short-lived but may include AV block, bronchospasm and seizures (usually at higher doses).

The class III drug amiodarone has been used for refractory dysrhythmias usually in combination with other drugs. Because of its significant prodysrhythmic effects, its use and administration should be monitored by someone specializing in the management of dysrhythmias. Amiodarone is a highly lipid-soluble antidysrhythmic agent with complex pharmacology. It is a noncompetitive inhibitor of both alpha and beta adrenergic receptors. Intravenous administration of amiodarone produces vasodilation and AV nodal suppression. Amiodarone inhibits the outward potassium current, which prolongs the QT interval. It also inhibits sodium channels, which slows conduction in the ventricular myocardium and prolongs QRS duration. For both SVT and ventricular dysrhythmias, a loading dose of 5 mgs/kg is recommended over several minutes to 1 hour. Repeated doses of 5 mgs/kg up to a maximum of 15 mgs/kg/day may be used as needed.

The main acute side effect is hypotension. Terminal elimination of amiodarone is very prolonged, with a half-life lasting up to 40 days. Potential long-term complications include hypo- or hyperthyroidism, interstitial pneumonitis, corneal microdeposits, blue-gray skin discoloration and elevated liver enzyme levels.

Amiodarone may be considered for refractory VF that persists despite three shocks. This drug has been used most commonly in children in the postoperative period after cardiac surgery. It is effective on ectopic atrial tachycardia or junctional ectopic tachycardia. Amiodarone is also effective for VT in postoperative patients or children with underlying cardiac disease. Amiodarone has been added as a drug to consider in pediatric pulseless arrest.

Verapamil, a calcium channel blocker (class IV) decreases conduction through the SA and AV nodes as well as decreasing spontaneous automaticity. It can be used in the older child for control or supraventricular dysrhythmias. It should not be used in the intravenous form in infants less than one year of age as it has been associated with sudden death, in this age group. It should not be given in combination with beta blockers, especially intravenously, as this can cause profound hypotension and bradycardia.

The number of antidysrhythmic agents is quite large. Although drugs are grouped within classes, there is significant variation within each group. Before any drug is given, the recommended dosage should be checked, the potential side effects reviewed and any suggested ill antidotes" (ex: calcium for verapamil) should be readily available.

Commonsense Approach to Management of Common Dysrhythmias (Flow charts 56.1 to 56.3)

Rhythm Disturbances can be Stable or Unstable

Stable rhythms include sinus tachycardia, supraventricular tachycardia in initial stages, atrial flutter, atrial fibrillation. Sinus tachycardia will require treatment of cause such as fever, pain, or hypovolemia as the case may be. Sinus tachycardia is an important sympathetic compensatory response particularly in patients with septic shock. Therefore, sinus tachycardia in sepsis should not be treated with beta blockers, digoxin or amiodarone. This can lead to severe bradycardia, hypotension and cardiac arrest.

Stable supraventricular tachycardia can be treated with vagal maneuvers, intravenous adenosine (0.1 mg/kg) and to be followed by intravenous digoxin (loading dose of 40 microgram/kg given in divided doses over 24 hours) (caution WPW syndrome in which case beta-blocker such as propranolol will be required). Other stable rhythms can be managed in consultation with a cardiologist.

Unstable rhythms need immediate attention. A knowledge of Defibrillation, cardioversion and temporary pacing is necessary.

Supraventricular tachycardia with conjestive heart failure, ventricular tachycardia, ventricular fibrillation, severe bradycardia and asystole (no rhythm, flat ECG) are unstable rhythms need immediate attention.

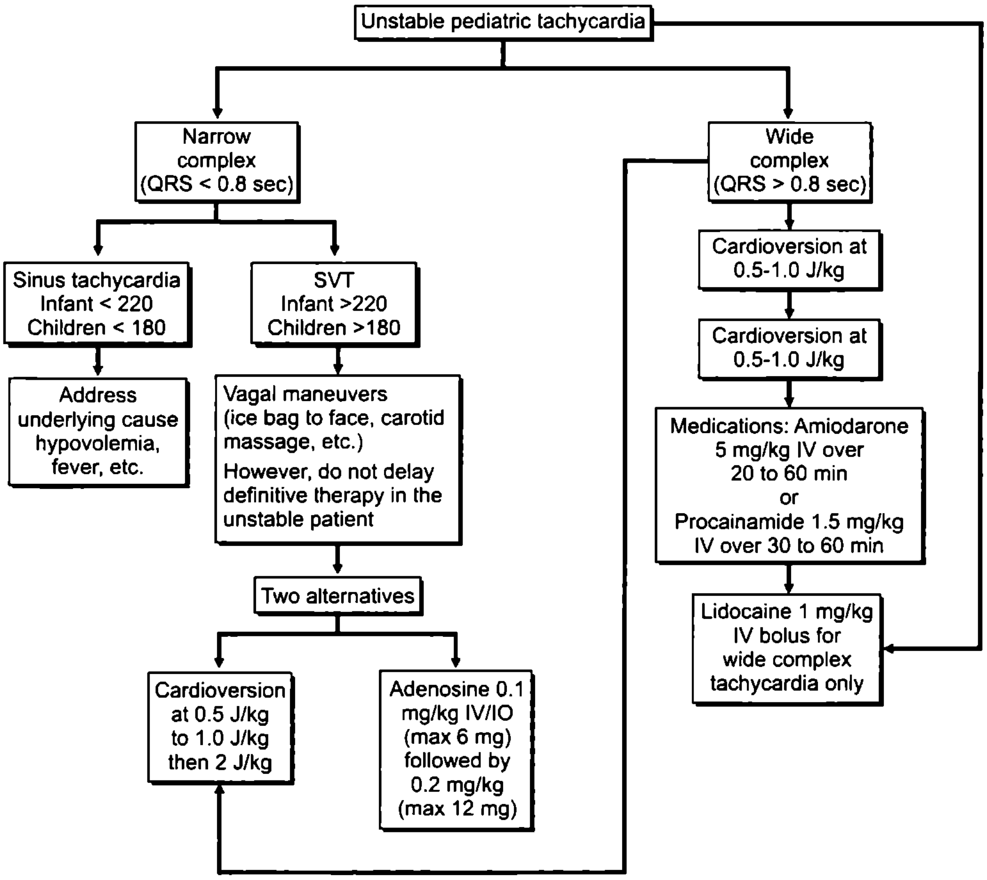
Airway should be secured, breathing initiated and cardiac compressions need to be instituted if heart rate is below 60 in children and 80 in a neonate, in pulseless ventricular tachycardia, electromechanical dissociation (or pulse less electrical activity, PEA) in asystole, and ventricular fibrillation. Epinephrine should be given for bradycardia, ventricular fibrillation and asystole as per PALS guidelines.

In case of unstable supraventricular tachycardia with lethargy, signs of cardiomegaly and congestive heart failure synchronized DC cardioversion (0.5 joules/kg) is indicated. In case of ventricular tachycardia, lidocaine 1 mg/kg intravenously should be given, if no improvement is seen, synchronized DC cardioversion (1 joule/kg) needs to be done. In pulse less ventricular tachycardia immediate DC cardioversian should be done.

In case of ventricular fibrillation, while performing cardiopulmonary resuscitation (CPR) defibrillation (1 to 2 joules/kg) needs to be done after administration of epinephrine which converts fine fibrillations to coarse fibrillation making it more amenable to defibrillation. Resistant ventricular fibrillation can be treated with intravenous amiodarone (5 mg/kg). Resistant ventricular fibrillation in a patient with renal failure could be due to hyperkalemia readily treated with intravenous calcium chloride.

Needless to say that epinephrine, lidocaine, and atropine should be readily available, so should be calcium chloride if severe hyperkalemia or calcium channel blocker toxicity is suspected. At any time during resuscitation if sinus bradycardia is seen, epinephrine or atropine can be given. For severe bradycardia pacing may be required (see Chapter on Cardiac Pacing). Antibradycardia or tachycardia devices may be implanted in resistant cases. Implantation of permanent pacemaker is required if *av* block following cardiac surgery persists longer than 14 days.

Flow chart 56.1: Pediatric tachycardia algorithm


Unstable pediatric tachycardia
Narrow complex (QRS < 0.8 sec)
Wide complex (QRS > 0.8 sec)
Sinus tachycardia Infant < 220 Children < 180
SVT Infant >220 Children >180
Address underlying cause hypovolemia, fever, etc.
Vagal maneuvers (ice bag to face, carotid massage, etc.) However, do not delay definitive therapy in the unstable patient
Two alternatives
Cardioversion at 0.5 J/kg to 1.0 J/kg then 2 J/kg
Adenosine 0.1 mg/kg IV/IO (max 6 mg) followed by 0.2 mg/kg (max 12 mg)
Cardioversion at 0.5-1.0 J/kg
Cardioversion at 0.5-1.0 J/kg
Medications: Amiodarone 5 mg/kg IV over 20 to 60 min or Procainamide 1.5 mg/kg IV over 30 to 60 min
Lidocaine 1 mg/kg IV bolus for wide complex tachycardia only

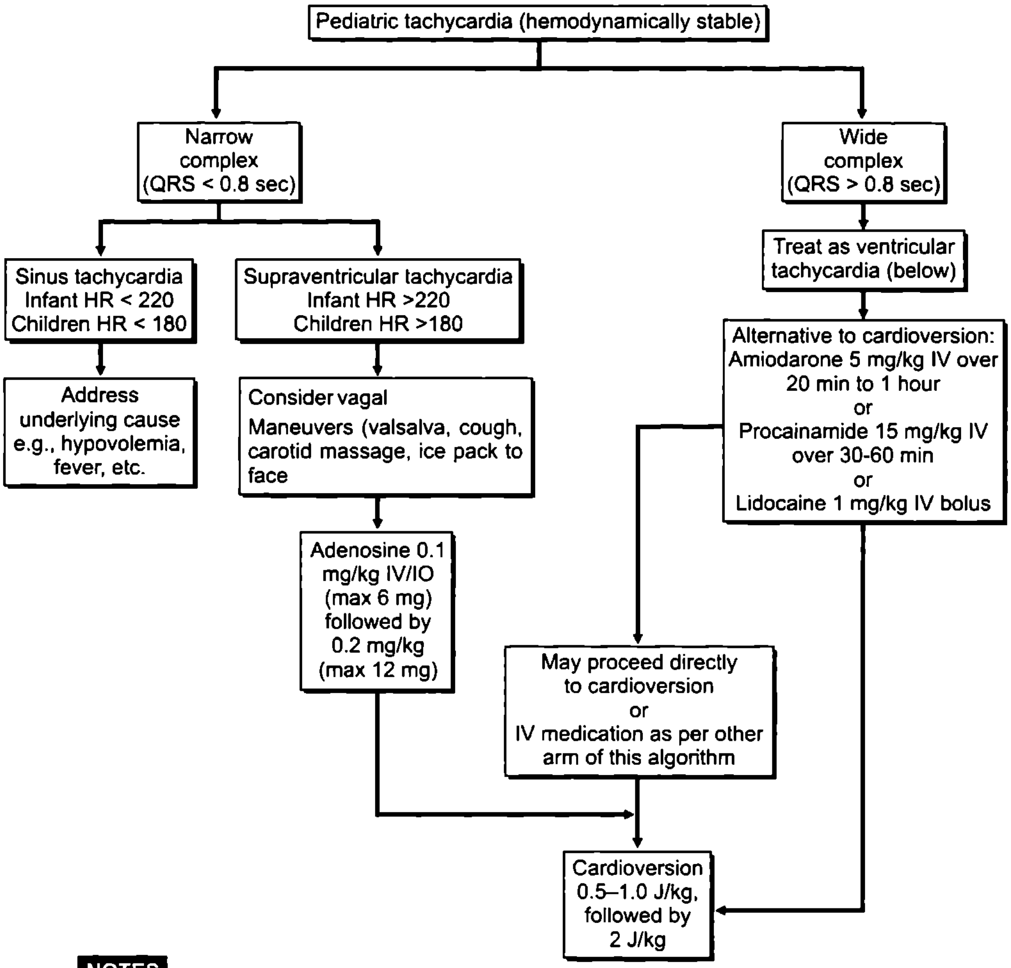
NOTES

Consider underlying causes including hypothermia, hypovolemia, cardiac tamponade, pulmonary embolism, hypoxia, tension penumothorax, acidosis, massive infarction, hyperkalemia, hypokalemia, overdose (beta blockers, calcium channel blockers, etc.) etc.

Unstable means signs and symptoms related to the rhythm (mental status changes, cyanosis, hypotension, etc.

Generally, amiodarone and procainamide should not be used together

Flow chart 56.2: Pediatric tachycardia algorithm (hemodynamically stable pediatric tachycardia)


Pediatric tachycardia (hemodynamically stable)
Narrow complex (QRS < 0.8 sec)
Wide complex (QRS > 0.8 sec)
Sinus tachycardia Infant HR < 220 Children HR < 180
Supraventricular tachycardia Infant HR >220 Children HR >180
Treat as ventricular tachycardia (below)
Address underlying cause e.g., hypovolemia, fever, etc.
Consider vagal Maneuvers (valsalva, cough, carotid massage, ice pack to face
Alternative to cardioversion: Amiodarone 5 mg/kg IV over 20 min to 1 hour or Procainamide 15 mg/kg IV over 30-60 min or Lidocaine 1 mg/kg IV bolus
Adenosine 0.1 mg/kg IV/IO (max 6 mg) followed by 0.2 mg/kg (max 12 mg)
May proceed directly to cardioversion or IV medication as per other arm of this algorithm
Cardioversion 0.5–1.0 J/kg, followed by 2 J/kg

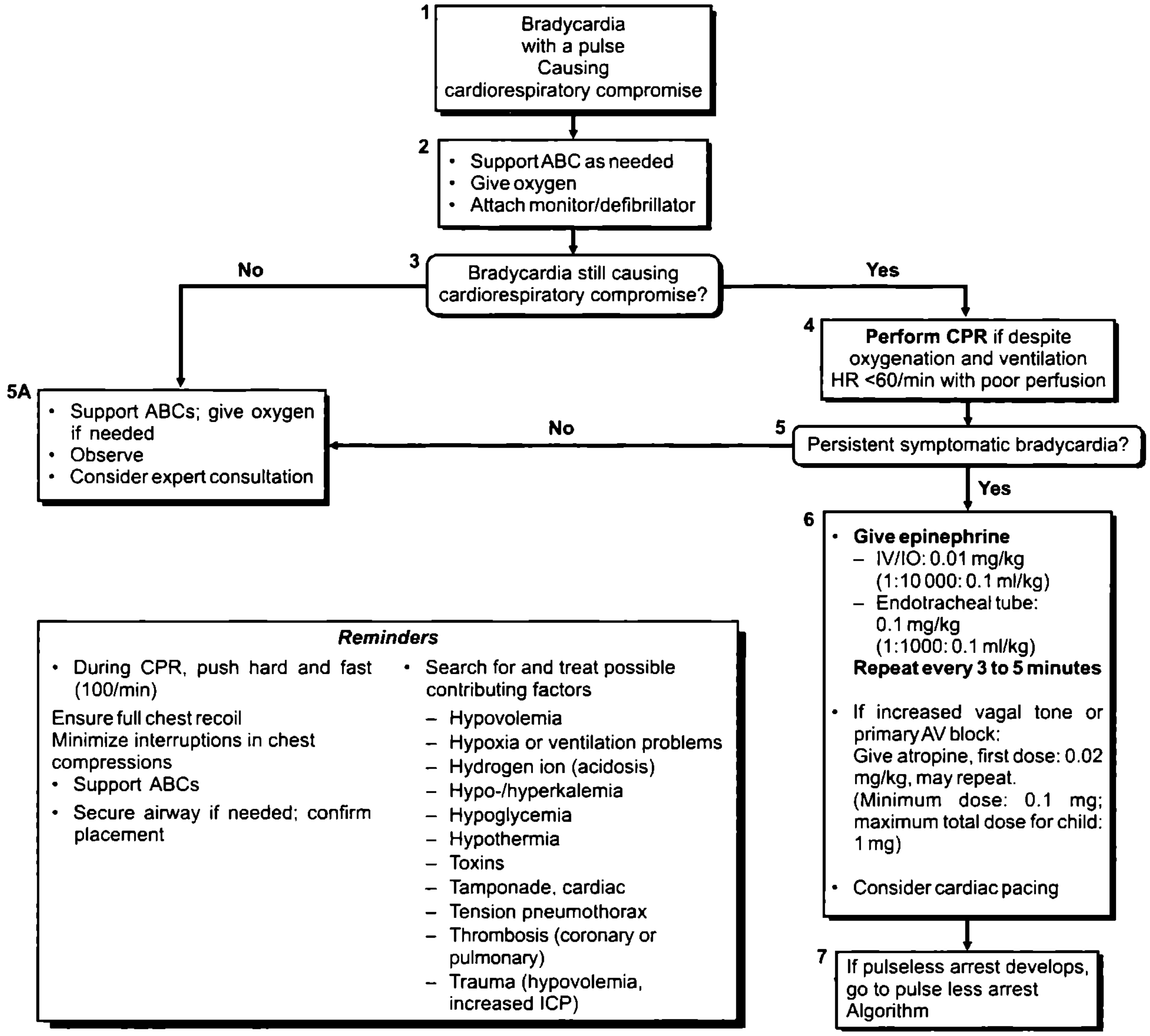
NOTES

Stable means no signs or symptoms of hypoperfusion such as mental status changes, cyanosis, hypotension, etc.

Consider underlying causes including hypothermia, hypovolemia, cardiac tamponade, pulmonary embolism, hypoxia, tension pneumothorax, acidosis, massive infarction, hyperkalemia, hypokalemia, overdose (beta blockers, calcium channel blockers, etc.) etc.

Consultation with pediatric cardiology is suggested before cardioversion

Flow chart 56.3: Bradycardia algorithm


1
Bradycardia with a pulse Causing cardiorespiratory compromise
2
• Support ABC as needed
• Give oxygen
• Attach monitor/defibrillator
3
Bradycardia still causing cardiorespiratory compromise?
No
Yes
4
Perform CPR if despite oxygenation and ventilation HR <60/min with poor perfusion
5A
• Support ABCs; give oxygen if needed
• Observe
• Consider expert consultation
No
5
Persistent symptomatic bradycardia?
Yes
6
• **Give epinephrine**
– IV/IO: 0.01 mg/kg (1:10 000: 0.1 ml/kg)
– Endotracheal tube: 0.1 mg/kg (1:1000: 0.1 ml/kg)
Repeat every 3 to 5 minutes
• If increased vagal tone or primary AV block: Give atropine, first dose: 0.02 mg/kg, may repeat. (Minimum dose: 0.1 mg; maximum total dose for child: 1 mg)
• Consider cardiac pacing
7
If pulseless arrest develops, go to pulse less arrest Algorithm

Reminders

- During CPR, push hard and fast (100/min)

Ensure full chest recoil
Minimize interruptions in chest compressions

- Support ABCs
- Secure airway if needed; confirm placement
- Search for and treat possible contributing factors
  - Hypovolemia
  - Hypoxia or ventilation problems
  - Hydrogen ion (acidosis)
  - Hypo-/hyperkalemia
  - Hypoglycemia
  - Hypothermia
  - Toxins
  - Tamponade, cardiac
  - Tension pneumothorax
  - Thrombosis (coronary or pulmonary)
  - Trauma (hypovolemia, increased ICP)

Lastly, remember, serum metabolic abnormalities related to potassium, calcium, magnesium, acidosis as well as hypothermia can lead to resistant dysrhythmias, necessitating treatment of the underlying disorder. JET (junctional ectopic tachycardia) that is resistant to treatment with digoxin or amiodarone may require cooling to treat the tachycardia.

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CHAPTER

Hypertension in Children

Prasanna C Tellis, Amit Varma, Prashant Pruthi

Hypertension is a significant problem in pediatric age group.The discussion that follows will address common etiologies and issues in management of hypertension in children with special emphasis of treatment common cause of hypertension in the pediatric intensive care unit (PICU).

Definitions

Hypertension in a pediatric patient is defined as systolic or diastolic blood pressure (BP) greater than 95th percentile for the age, sex and height.

High normal or borderline BP in a pediatric patient is defined as systolic or diastolic BP between 90th and 95th percentiles according to the categories of age, sex and height. Severe hypertension is defined as systolic and diastolic BP above 99th percentile. Table 57.1 shows normal ranges of blood pressure for different ages.

BP Measurement

Repeated BP monitoring should be done with the correct cuff size. Bladder of the cuff should cover 80-100 percent of circumference of the arm and the width should be approximately 40 percent of the circumference of the arm measured at a point midway between the olecranon and acromion. It is mandatory to record BP in all the 4 limbs with appropriate cuff to diagnose CoA (coarctation of aorta).

Etiology

Table 57.2 shows a list of various etiological agents and their relative frequency in pediatric age group. As evident from the list 80 percent of case of hypertension in children are related to renal or renovascular causes. 10 percent of patients have no demonstrable etiology, therefore labeled as essential hypertension. Patients with poliomyelitis, Guillain Barre syndrome,and familial dysautonomia may be hypertensive due to autonomic dysfunction and increased sympathetic activity. Children postrenal transplant and postcoarctation of aorta repair have hypertension in the postoperative period. Other common causes of transient hypertension in the PICU include trauma, pain, fear, anxiety, fluid overload,

Table 57.1: Normal values of vital signs in different age groups

Normal values	*Systolic BP/Diastolic BP*	*Pulse/ min*	*Resp/ min*
Neonate 3 kg birth	50-70 mmHg/25-45 mmHg	70-170	30-40
Neonate 96 hours	60-90 mmHg/20-60 mmHg	70-170	30-40
Infant 6 month	87-105 mmHg/53-66 mmHg	70-170	30-40
Toddler 2 years	95-105 mmHg/53-66 mmHg	80-130	25-32
School age 7 years	97-112 mmHg/57-71 mmHg	70-110	20-26
Adolescent 15 years	112-128 mmHg/66-80 mmHg	60-100	16-20

Table 57.2: Causes of hypertension

Causes	*Approximate relative incidence (%)*
Persistent hypertension	
Intrinsic renal disease	
Chronic glomerulonephritis	40
Chronic pyelonephritis	25
Obstructive uropathy	3
Other congenital lesions of kidney (Dysplastic, hypoplastic, Polycystic, medullary cystic necrosis)	
Renal tumors	< 1
Renovascular	
Renal artery stenosis	10
Renal arteritis with or without aortitis	5
Renal vein thrombosis	< 1
Endocrine causes	
Pheochromocytoma, neuroblastoma	
Adreno-genital syndrome, Cushing's-Disease, aldosteronism	1
Miscellaneous	
Essential hypertension	10
Other causes:	
Transient hypertension	
Renal	
Acute post-streptococcal glomerulonephritis,	
Hemolytic uremic syndrome	
Anaphylactoid purpura	
Postrenal transplant or urologic surgery.	
Other causes	
Postcoarctation repair	
Raised ICP, pain, anxiety, full bladder	
Administration of corticosteroids or contraceptives	
Hypernatremia, fluid overload	
Familial dysautonomia	
Porphyria hepatica	
Poliomyelitis	
Guillain–Barre syndrome	

steroid therapy, hypernatremia, full bladder, hemolytic uremic syndrome and raised intracranial pressure. Most causes of hypertension in the PICU are treatable by correcting the causative factors. Anti hypertensive agents are usually required in patients with cushings disease, adrenogenital syndrome, hemolytic uremic syndrome, renal artery stenosis and most patients with essential hypertension.

Hypertensive emergencies can occur in all patients with hypertension, specially in patients with pheochromocytoma (a tumor of adrenal medulla) and require emergent antihypertensive therapy with fast acting intravenous agents such as sodium nitroprusside and labetalol to prevent further complications such as intracranial bleeding.

Investigations

Routine basic investigations to be done in children with hypertension are:

- CBC
- BUN
- Creatinine
- Electrolytes
- Calcium
- Urinanalysis
- Urine culture
- Renal ultrasound
- CXR (Chest X-ray)

An echocardiogram and ECG should be routinely done to follow the heart size or detect any intracardiac abnormality or coarctation of aorta.

Depending on initial investigation reports further investigation that may be done are:

- IVP (Intravenous pyelography)
- Isotopic Renogram
- MCU (Micturiting Cystourethrogram)
- Renal arteriography
- CT/MRI of abdomen/adrenals
- MIBG scan, Renal biopsy
- Hormonal studies:
  - Plasma rennin activity
  - Serum aldosterone
  - Thyroid function tests
  - Urine catecholamines
  - Plasma and urine steroid profile
  - Vena cava catecholamines.

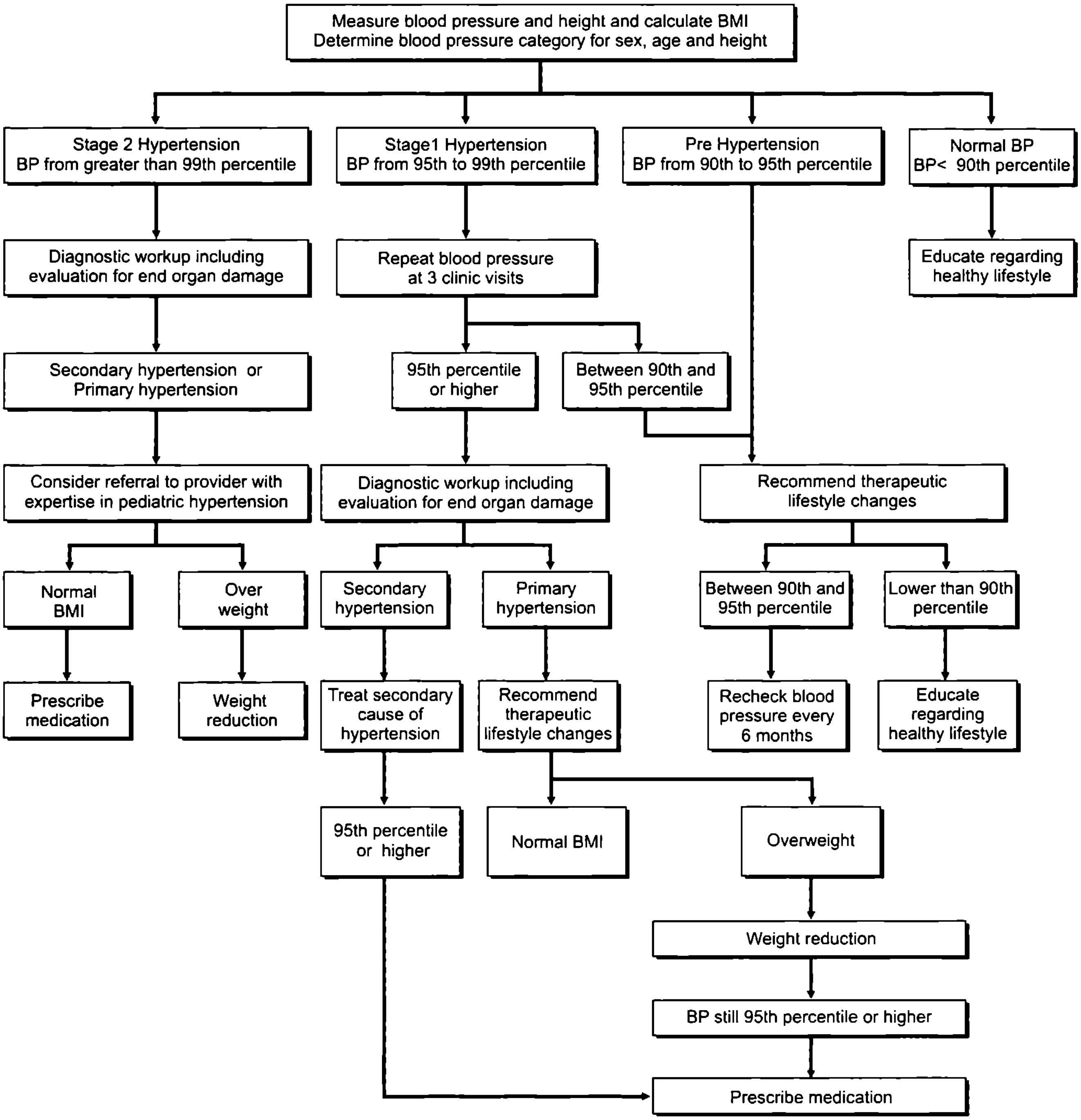
Nonpharmacological Management

In most children weight reduction, exercise prograr and dietary intervention will help with control c blood pressure (Flow chart 57.1).

Pharmacologic Therapy

Commonly used agents in the PICU are sedativ and analgesics to alleviate anxiety and pain. Las and fluid restriction is used in patients wi hypertension secondary to fluid retention, hype natremia and steroid use. ICP control measures ne

Flow chart 57.1: Approach to pediatric hypertension


Measure blood pressure and height and calculate BMI
Determine blood pressure category for sex, age and height
Stage 2 Hypertension
BP from greater than 99th percentile
Stage1 Hypertension
BP from 95th to 99th percentile
Pre Hypertension
BP from 90th to 95th percentile
Normal BP
BP< 90th percentile
Diagnostic workup including evaluation for end organ damage
Repeat blood pressure at 3 clinic visits
Educate regarding healthy lifestyle
Secondary hypertension or Primary hypertension
95th percentile or higher
Between 90th and 95th percentile
Consider referral to provider with expertise in pediatric hypertension
Diagnostic workup including evaluation for end organ damage
Recommend therapeutic lifestyle changes
Normal BMI
Over weight
Secondary hypertension
Primary hypertension
Between 90th and 95th percentile
Lower than 90th percentile
Prescribe medication
Weight reduction
Treat secondary cause of hypertension
Recommend therapeutic lifestyle changes
Recheck blood pressure every 6 months
Educate regarding healthy lifestyle
95th percentile or higher
Normal BMI
Overweight
Weight reduction
BP still 95th percentile or higher
Prescribe medication

to be used if hypertension is associated with bradycardia in a patient with head trauma, meningoencephalitis, or toxic ingestion. In patients with renal hypertension, enalapril, captopril, labetalol or nifedipine may be used (See Table 57.3 for dosage).

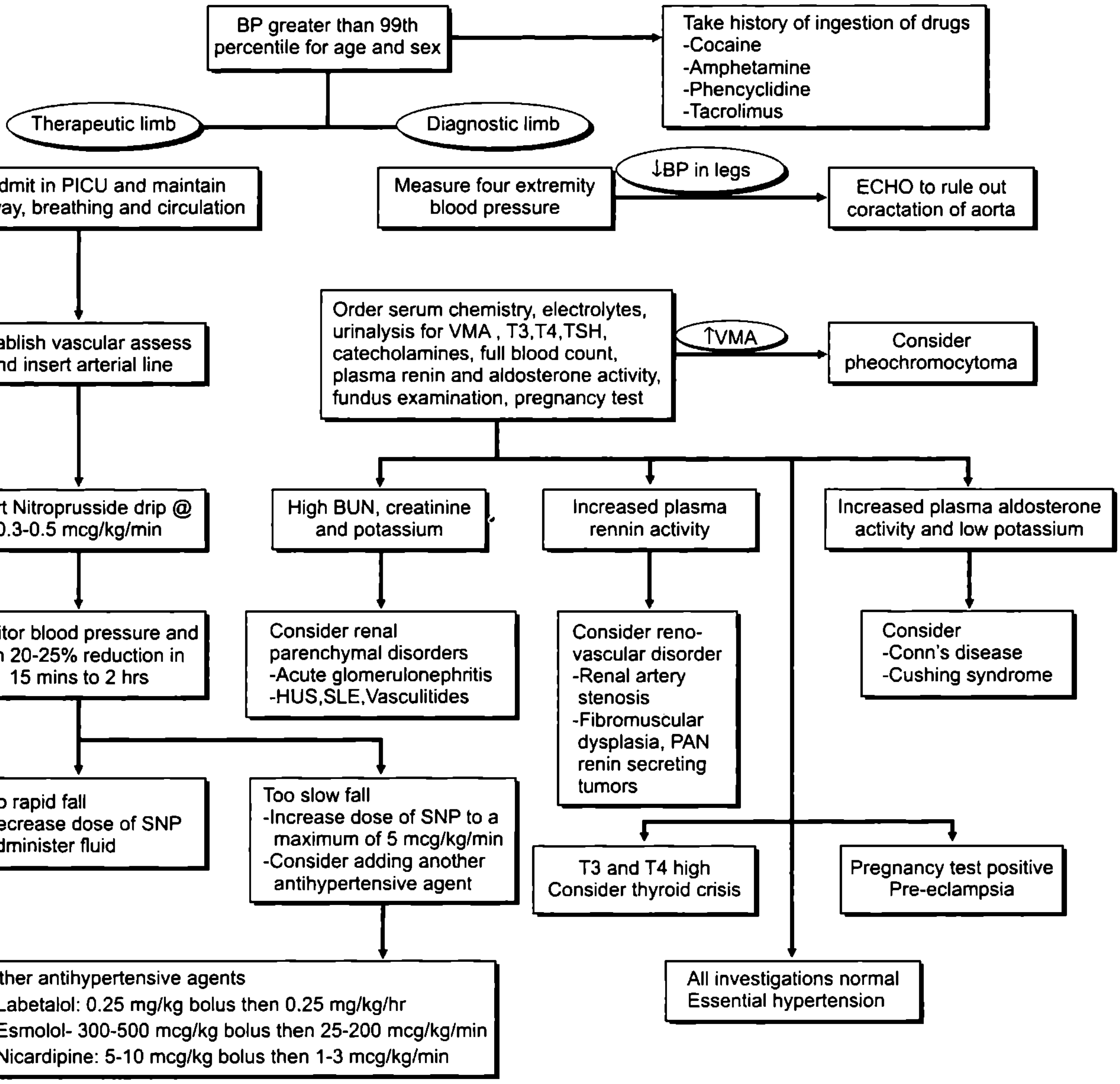
Hypertensive Emergencies

Drugs used as infusions in hypertensive emergencies are (Table 57.3):

- Sodium nitroprusside (SNP)
- Labetelol
- Nicardipine

Table 57.3: Antihypertensive agents

Drug	*Mechanism of action*	*Dosage range*	*Route*	*Duration*	*Side effects*
Vasodilators					
Hydralazine	Relax arteriolar smooth muscle	0.1-0.8 mg/kg/dose	IV	2-4 hr	Tachycardia, nausea
		0.5-2 mg/kg/day and increase to max 200 mg/24 hr	PO	6-8 hr	Drug induced lupus
Diazoxide	Relax smooth muscle	2.5 mg/kg/dose Max 100 mg	IV	6-24 hr	Tachycardia, hypotension Hyperglycemia
Nitroprusside	Dilatation of arterioles and venules	0.5-8.0 µg/kg/min	IV	Infusion	Thiocyanate production rarely Hypothyroidism
Minoxidil	Arteriolar dilatation	0.2-1.0 mg/kg/24 hr Max 50 mg/24 hr	PO	12-24 hr	Hypertrichosis, fluid retention
Nitroglycerine	Vasodilator	0.2 to 10 µg/kg/min	Infusion	3-5 min	Tachycardia
Adrenergic blockade					
Phentolamine	Alpha-receptor blockade	0.1 mg/kg/dose Max 5 mg	IV	1 hr	Reflex tachycardia
Phenoxybenzamine	Alpha-receptor blockade	2.5 mg/24 hr	PO	6-12 hr	Tachycardia may progress to arrhythmia
Prazosin	Alpha-receptor blockade	5 µg/kg initial dose, increase to 25 mg/kg/dose Max 15 mg/24 hr	PO	8-12 hr	First dose orthostatic hypotension
Propranolol	Beta-receptor blockade	0.025-0.1 mg/kg/dose	IV	6-8 hr	Bronchospasm, bradycardia.
	Reduces rennin release	0.5-5 mg/kg/day	PO	6-12 hrs	Vivid dreams.
Labetalol	Alpha and beta blockade	Titrate 0.2-2 mg/kg/hr	IV	Infusion	Orthostasis, dizziness, bronchospasm
Sympatholytic agents					
Alpha-Methyldopa	Alpha adrenergic blockade Decrease sympathetic tone	10 mg/kg/24 hr and increase to 65 mg/kg/24 hr	PO	6-8 hr	Sedation, hepatic dysfunction, positive coombs reaction
Clonidine	2-alpha agonist in CNS	3-5 µg/kg/dose	PO	6-8 hr	Sedation, constipation, rebound withdrawl hypertension
Renin-angiotension					
Captopril	Inhibition of converting enzymes	0.1-0.3 mg/kg/dose & increase to max 2 mg/kg/dose	PO	8 hr	Proteinuria neutropenia, rash
Enalapril	Same as captopril	0.1-0.5 mg/kg/dose	PO	12-24 hr	Hypotension
		5-10 µg/kg/dose	IV	8-12 hr	Transient hypotension
Calcium channel					
Nifedipine	Calcium channel blocker	0.2-0.5 mg/kg/dose Max 10 mg/dose	PO	repeat 4-6 hr	Facial flushing, tachycardia
Verapmil	Calcium channel blocker	40-80 mg/dose	PO	8 hrs	avoid below 1 year.
Nicardipine	Calcium channel blocker	1-3 mg/kg/min	IV		
Diuretic agents					
Hydrochlorothiazide	Diuresis	1-2 mg/kg/24 hr	PO	12-24 hr	Hypokalemia, Hyperuricemia, Hypercalcemia.
Furosemide	Diuresis	1 mg/kg/dose	IV	4-6 hr	Hypokalemia,
		2 mg/kg/dose	PO	4-6 hr	alkalosis



Flow chart 57.2: Approach to hypertensive crisis

BP greater than 99th percentile for age and sex
Take history of ingestion of drugs
-Cocaine
-Amphetamine
-Phencyclidine
-Tacrolimus
Therapeutic limb
Diagnostic limb
Admit in PICU and maintain airway, breathing and circulation
Measure four extremity blood pressure
↓BP in legs
ECHO to rule out coractation of aorta
Establish vascular assess and insert arterial line
Order serum chemistry, electrolytes, urinalysis for VMA , T3,T4,TSH, catecholamines, full blood count, plasma renin and aldosterone activity, fundus examination, pregnancy test
↑VMA
Consider pheochromocytoma
Start Nitroprusside drip @ 0.3-0.5 mcg/kg/min
High BUN, creatinine and potassium
Increased plasma rennin activity
Increased plasma aldosterone activity and low potassium
Monitor blood pressure and aim 20-25% reduction in 15 mins to 2 hrs
Consider renal parenchymal disorders
-Acute glomerulonephritis
-HUS,SLE,Vasculitides
Consider reno-vascular disorder
-Renal artery stenosis
-Fibromuscular dysplasia, PAN renin secreting tumors
Consider
-Conn's disease
-Cushing syndrome
Too rapid fall
-Decrease dose of SNP
-Administer fluid
Too slow fall
-Increase dose of SNP to a maximum of 5 mcg/kg/min
-Consider adding another antihypertensive agent
T3 and T4 high
Consider thyroid crisis
Pregnancy test positive
Pre-eclampsia
Other antihypertensive agents
- Labetalol: 0.25 mg/kg bolus then 0.25 mg/kg/hr
- Esmolol- 300-500 mcg/kg bolus then 25-200 mcg/kg/min
- Nicardipine: 5-10 mcg/kg bolus then 1-3 mcg/kg/min
All investigations normal
Essential hypertension

- Esmolol
- Nitroglycerine (TNG)

Sodium nitroprusside is a potent fast acting antihypertensive agent used as continuous infusion started at 0.5 to 1 μgm/kg/min titrated slowly to bring the blood pressure down. Rapid infusions may lead to a precipitous fall in blood pressure. Exposure to sunlight should be avoided. Sodium nitroprusside can cause cyanide toxicity, hence long term infusions (longer than a day) require monitoring of thiocyanate levels. A combination of nitroglycerin and nitroprusside is used for afterload reduction post-cardiac surgery (Flow chart 57.2).

Invasive arterial monitoring is mandatory while treating hypertensive emergencies with sodium nitro-prusside infusions.

Other drugs used as boluses in hypertensive emergencies are:

- Nifedipine
- Diazoxide
- Labetalol
- Hydralazine
- Enalapril
- Esmolol
- Nicardipine depending on availability

CHAPTER

Postoperative Management of Pediatric Cardiac Patients after Open Heart Surgery

Vikas Taneja, Praveen Khilnani

INTRODUCTION

The incidence of congenital heart disease is about 1% globally. Earlier the major management of patients with complex heart diseases was mainly palliative but now improvements in cardiopulmonary bypass techniques, surgical procedures and post operative care have made early neonatal repair possible for most congenital heart defects.[1] The major focus in the last 10-15 years has been on a coordinated, multidisciplinary approach, which requires the involvement of pediatric cardiologists, pediatric cardiac surgeons, pediatric intensivists, pediatric cardiac anesthesiologists, perfusionists and specialized nurses. This chapter discusses the post operative management of children with congenital heart diseases with focus on basic physiological principles in pediatric cardiology, the effects and management strategies after cardiopulmonary bypass and specific situations like low cardiac output, life threatening arrhythmias. The management of specific groups of heart defects has also been discussed briefly.

BASIC PHYSIOLOGIC PRINCIPLES FACTORS AFFECTING CARDIAC OUTPUT

The cardiac output (CO) is dependent on stroke volume (SV) and heart rate (HR). The SV further depends on the preload, myocardial contractility and afterload.[2]

Preload, defined as the degree of end-diastolic fiber stretch, determines the end-diastolic volume. This in turn is influenced by the intravascular volume status of the patient and ventricular wall thickness. For clinical purposes, the central venous pressure (CVP) is a reasonable reflection of the preload status.

Myocardial contractility is characterized by the force and velocity of myocardial contraction, but, clinically the contractile state is often expressed as ejection fraction (LVEF).

Afterload, the force resisting myocardial fiber shortening after stimulation from the relaxed state, is a reflection of the work the myocardium has to do. Clinically, the afterload is referred to as the resistance against which the heart has to function.

The **HR and rhythm** are also important contributors to cardiac output. If heart rate becomes too high or irregular, it leads to shorter cardiac cycles, less cardiac filling during diastole and thus low cardiac output.

The **Hb levels and PaO_2** are also important contributors to cardiac output. They determine the oxygen delivery to the tissues which is the ultimate result of maintaining normal cardiac output, i.e preservation of adequate oxygen delivery to vital organs.

Factors Affecting Myocardial Performance

Under most circumstances, the CO is directly proportional to the amount of blood coming into it. This is a direct effect of the muscle stretch, which results in muscle to contract with a greater force. This is the **Frank-Starling principle.** This mechanism operates in AHF, but as ventricular function is abnormal, the response is inadequate. If the Frank-Starling curve is depressed, fluid retention, vasoconstriction, and a cascade of neurohumoral responses lead to poor myocardial performance. Over time, LV remodeling with dilatation and hypertrophy further compromises cardiac performance, especially during physical stress.[3,4]

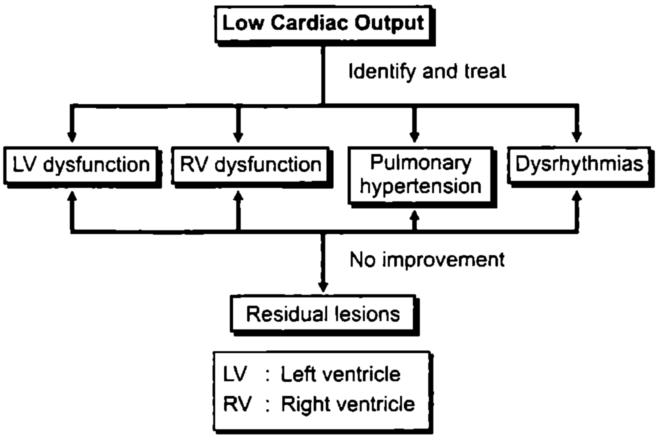
Pathophysiology of Low Cardiac Output Based on Etiology (Flow chart 58.1)

On the basis of etiology, low cardiac output may be due to:

1. **Increased preload** may stretch the muscle fiber beyond physiologic states resulting in an effective decrease in cardiac function. This is seen in volume loading conditions like L – R shunts, mitral regurgitation, aortic regurgitation and complete heart block (unusually increased end diastolic volume due to a highly prolonged diastole.)
2. **Impaired myocardial contractility** results in a decreased myocardial function as in transposition of great arteries and anomalous left coronary artery from pulmonary artery (ALCAPA).
3. **Increased afterload:** when ventricles work against abnormally high afterload that result in myocardial failure and low cardiac output, e.g. Coarctation of aorta (CoA), aortic stenosis, interrupted aortic arch.
4. **Inadequate diastolic filling** would result in a low cardiac output due to decreased filling. This would typically be seen in tachyarrhythmias, constrictive pericarditis and severe ventricular hypertrophy.

Depending upon the cardiac lesion, left ventricular or right ventricular dysfunction may occur resulting in low cardiac output. These pathophysiologic states may affect the postoperative period also. Thus a thorough knowledge of the type of cardiac lesion, the preoperative magnitude of dysfunction, the type of surgical procedure undertaken and any intra operative events that might have occurred is required. Finally the cardiac performance in the immediate postoperative period is essential to determine the course of management. Going into the details of the cardiac lesions is beyond the scope of this chapter. Intensive care management requires knowing the type of ventricular dysfunction present preoperatively or post-operatively.[5,6]

Flow chart 58.1: Postoperative low cardiac output



Pathophysiology of Left Ventricle (LV) Dysfunction

In LV dysfunction, as the CO declines, the left atrial pressure increases resulting in an increase in pulmonary venous pressure. When fluid extravasates into the interstitial space and alveoli, it significantly alters pulmonary mechanics and, results in ventilation/perfusion mismatch. This results in intrapulmonary shunting of unoxygenated blood, decreasing mixed pulmonary capillary PO_2. Besides adjustments in inotropes, postoperative LV dysfunction is benefited by ventilatory maneuvers.[7]

Pathophysiology of Right Ventricle (RV) Dysfunction

In RV dysfunction, systemic venous congestive signs develop. Central venous pressure increases, which reflect the high RV end diastolic pressures. Pleural effusions usually accumulate in the right hemithorax and later bilaterally. Hepatic dysfunction commonly occurs secondary to RV failure, with increase in bilirubin, prothrombin time, and hepatic enzymes (e.g., AST, ALT). Reduced aldosterone breakdown by the impaired liver further contributes to fluid retention. Besides adjustments in inotropes, increasing ventilatory parameters usually worsen the postoperative RV dysfunction.[8]

Cardiopulmonary Bypass

Cardiopulmonary bypass (CPB) in neonates, infants and children differs substantially from that in adults.[9] Pediatric patients are exposed to biologic extremes including deep hypothermia, hemodilution, low perfusion pressures, wide variation in pump flow rates and wide ranging blood pH management. Pathophysiologic changes that occur during and after

CPB relate to the non endothelized bypass circuit and oxygenator, hypothermia, the degree of hemodilution, non pulsatile perfusion, age of the patient, the preoperative myocardial substrate, the length of the ischemic period on the myocardium (cross clamp time), the type of anesthesia used and the exaggerated inflammatory response present in the young child. The effects on the patient are both global and organ specific. The effects of cardiopulmonary bypass have been described as a whole body inflammatory response because of generalized activation of complement, neutrophils, cytokines and other inflammatory mediators. Most of the problems in the cardiac ICU are actually the sequelae of the bypass. This section discusses the effects of cardiopulmonary bypass and the causes and recognition of abnormal convalescence.

Myocardial Effects

The congenital heart defects repaired on CPB require a period of time during which the circulation to the heart is interrupted by aortic cross clamping and the administration of cardioplegia. Ischemic injury to the myocardium during the operative repair can present a major problem in the postoperative period. Therefore, for the intensivist the knowledge of the cross clamp time and the period of total circulatory arrest are very important. Depressed ventricular function in the postoperative period requires treatment by inotropes and in severe cases, ventricular assist devices.

CNS Effects

The likelihood of poor neurological outcome may be increased in infants exposed to deep hypothermic circulatory arrest, a technique in which the CPB is stopped after cooling the body to temperatures of 15-18°C. Neonates and infants exposed to CPB should be observed for neurological symptoms in the postoperative period especially seizures. These seizures are usually self limiting and reversible unless they are focal in origin related to micro emboli related to CPB, especially air emboli. Treatment is with an anticonvulsant, i.e. phenobarbitone or phenytoin. Because of the negative inotropic effects the anticonvulsant loading should be given judiciously and under strict monitoring.[10]

Pulmonary Effects

Pulmonary dysfunction is a common occurrence after CPB. Widespread inflammatory response with mediator release and platelet aggregation results in increased pulmonary vascular resistance (PVR), extravascular lung water and airway resistance.[11] Pulmonary function testing after CPB demonstrates a reduced static and dynamic compliance, end expiratory lung volumes, microatelectasis and an increase in the alveolar arterial oxygen gradient. Microatelectasis causes ventilation – perfusion mismatch which results in decrease in the blood oxygen content. Therapy is directed towards reducing atelectasis and improving ventilation perfusion mismatch. Patients after CPB require higher levels of positive end expiratory pressure (PEEP) to recruit end expiratory lung volumes. Care must be taken to avoid higher levels of PEEP, which may compromise cardiac output by decreasing the venous return to an already compromised heart.

Renal Effects

CPB with hypothermia, non-pulsatile perfusion and reduced mean arterial pressures causes release of renin, angiotensin, catecholamines and antidiuretic hormone. These circulating hormones result in decreased pulmonary blood flow. Apart from this the low cardiac output state after cardiac surgery can also result in decreased renal blood flow resulting in renal failure.[12] The clinical diagnosis of renal failure should be made early by demonstration of reduction in the urine output to less than 1 ml/kg/hr, or even an increase in the serum creatinine to double the baseline value. Treatment for renal dysfunction includes increasing the renal perfusion pressure by inotropes. Diuretics are primary agents for promoting urine output after CPB.[13] Diuretics should be used with caution in the immediate postoperative period because of ongoing capillary leak. Fulminant post-operative renal failure is primarily related to decreased cardiac output. Temporary support of these patients includes peritoneal dialysis and continuous veno venous hemofiltration (CVVH). For this reason the peritoneal dialysis catheter is usually placed postoperatively so that it can be used if required.

Electrolyte Abnormalities

The electrolyte and metabolic changes occurring in the postoperative period are seen with other types of surgical stress also like sodium and water retention, potassium loss and abnormalities in glucose metabolism. Initial fluid management consists of ¼ the normal maintenance usually sodium free with boluses of normal saline as and when required to maintain the CVP. Potassium is usually added after 24 hrs and when oliguria has resolved.[14]

GI/ Nutritional Effects

Nutrition is an essential component of postoperative management and feedings are usually begun once good bowel sounds are present. In case of unstable hemodynamics, feeds are usually delayed because of the risk of necrotizing enterocolitis. Patients who cannot tolerate enteral feeds are usually started on TPN.[15]

Postoperative Management

Evaluation

Evaluation in the pediatric cardiac intensive care unit requires physical examination, along with noninvasive and invasive hemodynamic monitoring to assess the cardio respiratory status.

Physical examination is an essential part of the evaluation after cardiac surgery. This should include the distal extremity temperature, capillary refill, pulse rate and volume, along with the direct auscultation of the lungs and the heart. A simple combination of capillary refill, peripheral temperature and pulse volume helps a lot in deciding the cardiorespiratory status and the type of intervention required. Other indicators of end organ function include consciousness level, urine output, ventilatory requirements, blood pressures, pH and lactic acidosis.

Noninvasive monitoring includes pulse oximetery, central and peripheral temperatures, ECG, BP. Falling peripheral temperature with normal or rising core temperature suggests decreasing and inadequate cardiac output. Pulse oximetery is an important tool to assess the oxygenation status of a postoperative cardiac patient.[16] A fall in the SpO_2 may be the first indication of the poor perfusion, or the poor ventilatory status or cardiac output.

Invasive Hemodynamic Monitoring

Invasive monitoring is an important tool for postoperative cardiac patient but must be used after determining the risk-benefit ratio. The risks associated with catheter placement may be higher in infants as compared to adults especially the risk of displacement, infection and thrombosis. Vascular catheters, which are placed in the operating room, include central venous, arterial, right atrial, left atrial and pulmonary artery catheters.[17] Various combinations of the above pressures help in assessing the cardiac status and accordingly the interventions done. Table 58.1 shows the interpretation of various pressures in biventricular repairs. The interpretation for univentricular repairs is discussed in the section on single ventricle complexes.

CVP or the right atrial pressures – provide information about the right sided filling pressures, the tricuspid valve function and cardiac output (mixed venous oxygen saturation)

Left atrial pressures – provide information about the left sided filling pressures (systolic or diastolic dysfunction), the mitral valve function, and presence of right to left shunting in the lungs.

Pulmonary artery catheters – provide information about the pulmonary pressures, pulmonary artery saturations and the cardiac output by thermodilution technique.

Arterial catheters – provide direct measurement of the blood pressure, continuous monitoring as well as sampling for blood gases, electrolytes, glucose, lactic acidosis, and hematocrit.

Laboratory Tests

Serial evaluation of laboratory tests is necessary after surgery which includes blood gases, lactates, ionized calcium, hematocrit, electrolytes, glucose, liver and renal functions.

Arterial blood gases provide information on oxygen delivery, CO_2 removal and acid base status, which ultimately reflect the tissue perfusion. Lactate is a

Table 58.1: Interpretation of various invasive pressures in a postoperative cardiac patient with low cardiac output

Clinical signs: Tachycardia, Poor perfusion, Hypotension, Cold extremities, Low urine output

ABP	*CVP*	*LAP*	*PAP*	*Interpretation*	*Action*
Low	Low	Low	Normal	Low Intravascular volume	Give fluids
Low	High	Low	Normal	RV Dysfunction	Decrease preload, Increase contractility – inotropes and decrease afterload – milrinone, inhaled nitric oxide, optimize HR, ventilatory manipulations – to decrease pulmonary vascular resistance
Low	High (Back pressure effect)	High	High (Back pressure effect)	LV Dysfunction	Increase contractility and decrease afterload – inodilator, keep HR towards upper side of normal, Electively ventilate, Decrease preload – diuretic if blood pressures permit,
Low	High	Low	High	Pulmonary Hypertension	Sedate, paralyze, hyperventilate, correct acidosis, hypoxia and hypercarbia, avoid painful stimuli, suctioning

ABP: Arterial blood pressure, CVP: Central venous pressure, LAP: Left atrial pressure, PAP: Pulmonary artery pressure, RV: Right ventricle, LV: Left ventricle, HR: Heart rate

very sensitive indicator of tissue perfusion in the immediate postoperative period and serial measurements help in assessing the cardiac output.[18]

The role of **ionized calcium** is important in neonates as their heart is more dependent on ionized calcium for effective contractility due to lack of intracellular transport system. Ionized calcium may be decreased in the post-operative period due to the use of citrated blood products. Moreover total calcium levels do not correlate with the ionized calcium after cardiopulmonary bypass due to rapid fluid shifts so ionized calcium levels is important after cardiopulmonary bypass.[19]

Hematocrit in the postoperative period is an indicator of ongoing bleeding or hemoconcentration due to capillary leak. Hematocrit needs to be maintained to improve oxygen delivery to the tissues.[20]

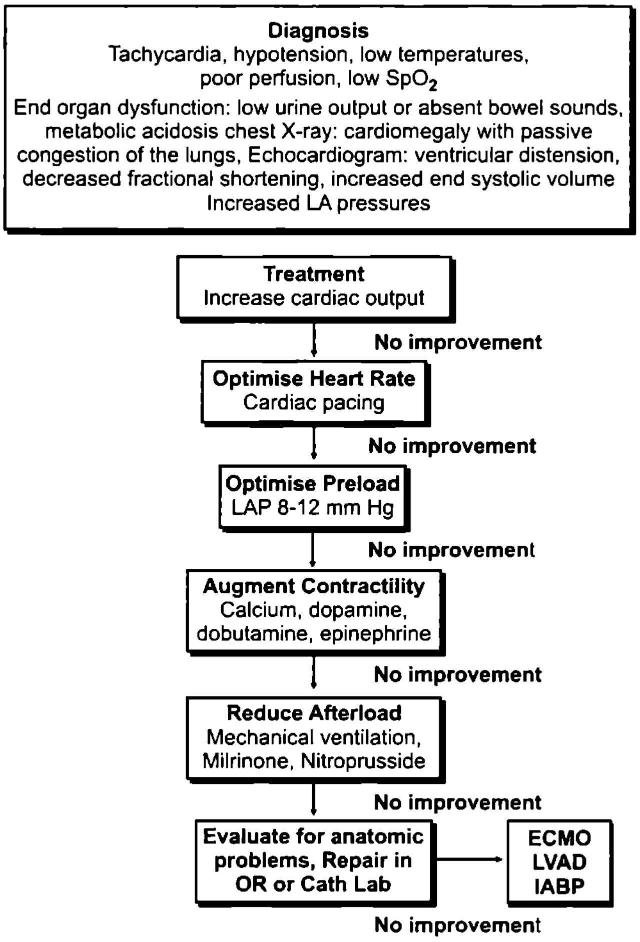
Electrolytes particularly potassium is important in the immediate postoperative period as it leads to rhythm disturbances. Hypokalemia needs to be recognized and corrected early to improve the effective cardiac output. It is usually decreased due to excessive diuresis post-CPB or drugs such as furosemide. Hyponatremia and hyperglycemia are stress related and are usually self correctable in the postoperative period.[21]

Specific Cardiac Issues

Four primary postoperative disturbances occur in the postoperative period that may lead to low cardiac output.

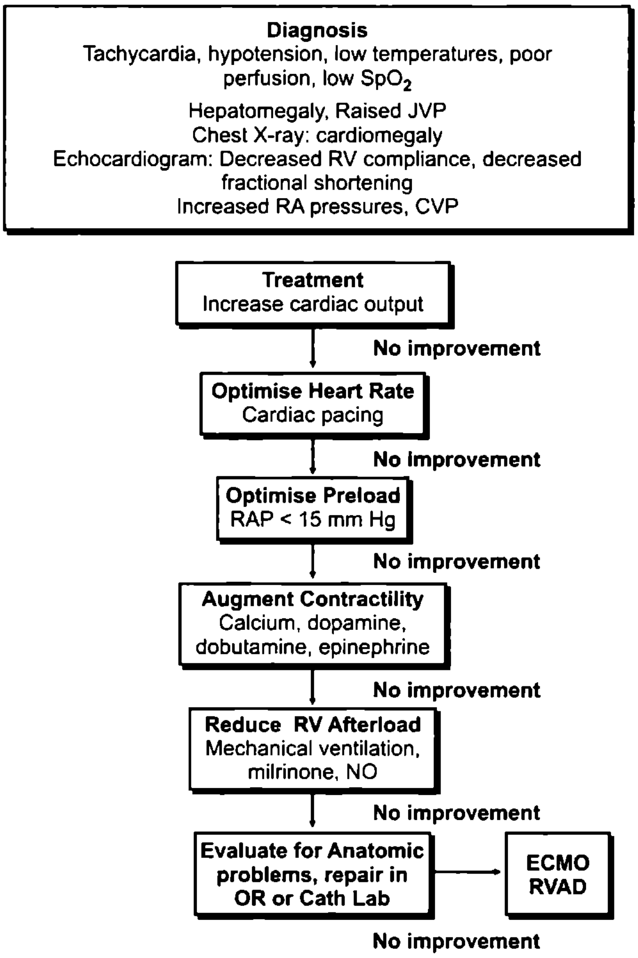
LV dysfunction (Flow chart 58.2): LV dysfunction can be seen after any cardiac surgery and is more easily diagnosed and treated than RV dysfunction. The cause is usually multifactorial and includes the preoperative conditions of the myocardium (LV hypertrophy, LV systolic/diastolic dysfunction) or response to alteration in the loading conditions of the heart (increase/decrease in preload/ afterload). The patient presents with tachycardia, hypotension and poor peripheral perfusion. SpO_2 is low due to poor peripheral perfusion. Chest X-ray (CXR) shows cardiomegaly with passive congestion of the lungs. Echocardiogram (ECHO) may demonstrate ventricular distension, decreased fractional shortening, decreased ejection fraction or increased end systolic volume. LA catheter placed during surgery will reveal increased LA pressure indicating increased LV end diastolic pressures. AB demonstrates metabolic and lactic acidosis Congestion of the lungs will result in decrease ventilation perfusion mismatch leading to hypoxemi and or hypercarbia. Because of low cardiac outpu

Flow chart 58.2: Left ventricular dysfunction


Diagnosis
Tachycardia, hypotension, low temperatures, poor perfusion, low SpO2
End organ dysfunction: low urine output or absent bowel sounds, metabolic acidosis chest X-ray: cardiomegaly with passive congestion of the lungs, Echocardiogram: ventricular distension, decreased fractional shortening, increased end systolic volume
Increased LA pressures
Treatment
Increase cardiac output
No improvement
Optimise Heart Rate
Cardiac pacing
No improvement
Optimise Preload
LAP 8-12 mm Hg
No improvement
Augment Contractility
Calcium, dopamine, dobutamine, epinephrine
No improvement
Reduce Afterload
Mechanical ventilation, Milrinone, Nitroprusside
No improvement
Evaluate for anatomic problems, Repair in OR or Cath Lab
ECMO
LVAD
IABP
No improvement

SpO_2	:	Oxygen saturation
OR	:	Operating room
LA	:	Left atrium
LAP	:	Left atrial pressure
ECMO	:	Extra corporeal membrane oxygenation
LVAD	:	Left ventricular assist device
IABP	:	Intra aortic balloon pump

Flow chart 58.3: RV dysfunction


Diagnosis
Tachycardia, hypotension, low temperatures, poor perfusion, low SpO2
Hepatomegaly, Raised JVP
Chest X-ray: cardiomegaly
Echocardiogram: Decreased RV compliance, decreased fractional shortening
Increased RA pressures, CVP
Treatment
Increase cardiac output
No improvement
Optimise Heart Rate
Cardiac pacing
No improvement
Optimise Preload
RAP < 15 mm Hg
No improvement
Augment Contractility
Calcium, dopamine, dobutamine, epinephrine
No improvement
Reduce RV Afterload
Mechanical ventilation, milrinone, NO
No improvement
Evaluate for Anatomic problems, repair in OR or Cath Lab
ECMO
RVAD
No improvement

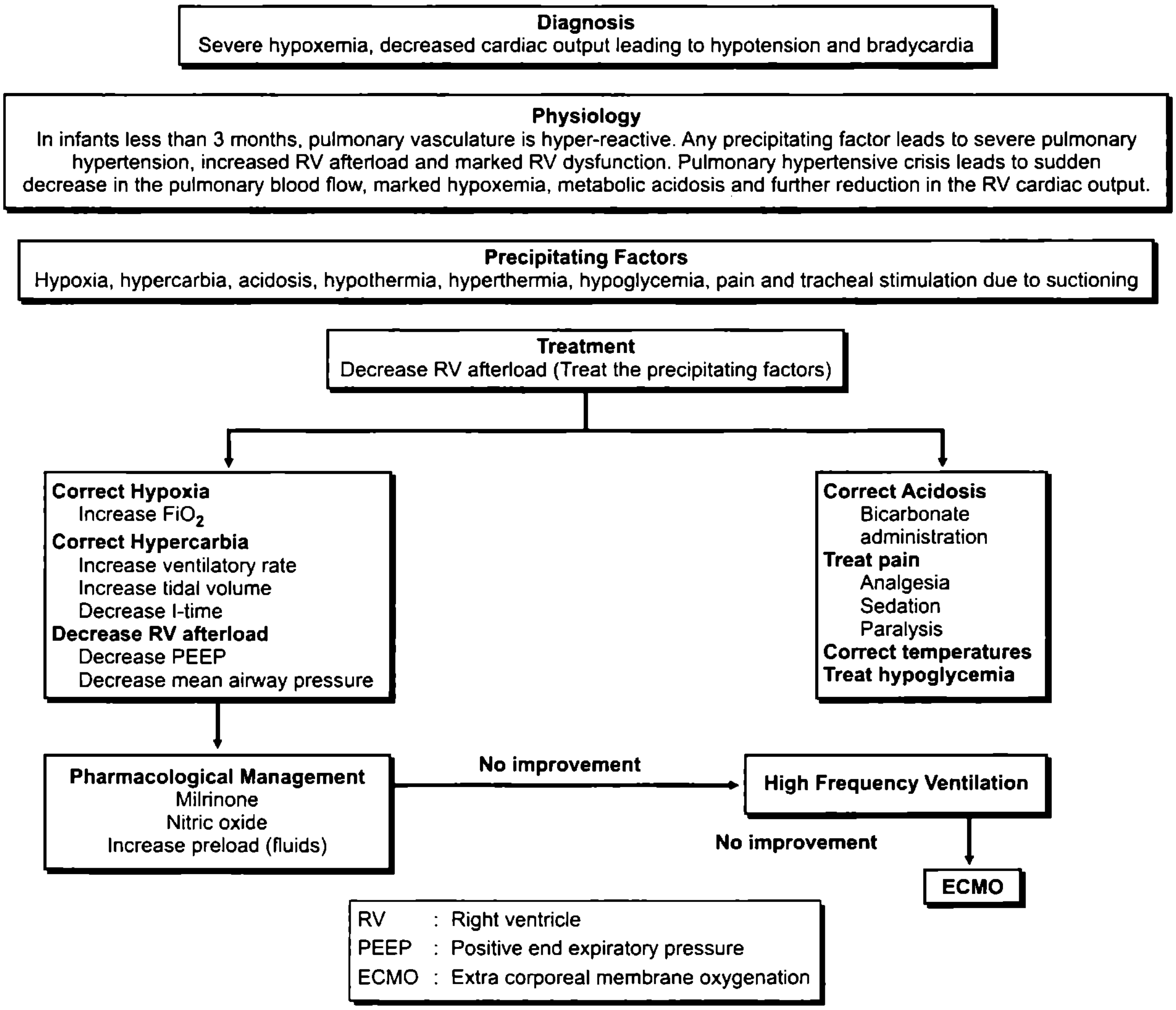
CVP	:	Central venous pressure
JVP	:	Jugular venous pressure
NO	:	Nitric oxide
ECMO	:	Extra corporeal membrane oxygenation
RVAD	:	Right ventricular assist device
RAP	:	Right atrial pressure
RV	:	Right ventricle

there may be evidence of end organ dysfunction in the form of low urine output or absent bowel sounds. Since cardiac output is a function of stroke volume and heart rate, optimizing these parameters will improve the cardiac output.[22]

RV dysfunction (Flow chart 58.3): RV dysfunction can be seen after any cardiac surgery. RV dysfunction should be considered in any patient in whom the RV incision had been used for repair or in whom the RV was abnormal before repair. The patient presents with signs of decreased systemic cardiac output because the LV will eject that portion of the blood presented to it by the RV. This manifests as tachycardia, hypotension and poor peripheral perfusion. SpO_2 is low due to poor peripheral perfusion. Echocardiogram demonstrates decreased RV shortening and abnormal compliance. RA pressures will be high as seen by increased CVP and will cause hepatic congestion. The treatment of RV dysfunction is aimed at improving the oxygen delivery in a similar way that of LV dysfunction. The RV is less sensitive to conventional inotropes than LV, so preload and afterload are more commonly manipulated to augment cardiac output.[23]

Pulmonary Hypertensive Crisis (Flow chart 58.4): Pulmonary arterial hypertension is a frequent postoperative condition, especially in neonates and infants less than 3 months of age. This is because of increased muscularization of the pulmonary arterioles and marked reactivity of the pulmonary arterioles. In addition the conditions that lead to increased pulmonary blood flow are at risk for pulmonary hypertension post-operatively. Patients with pulmonary hypertension develop marked RV dysfunction as a result of increased RV afterload. Pulmonary hypertensive crisis leads to sudden decrease in the pulmonary blood flow, leading to marked hypoxemia, metabolic acidosis and further reduction in the RV cardiac output. Therapy for pulmonary hypertensive crisis begins with prevention. Stimuli such as hypoxia, hypercarbia, acidosis, hypothermia, hyperthermia, hypoglycemia, pain and tracheal stimulation, which may trigger the crisis, should be avoided. In the post-operative period the patients should be kept deeply sedated and pain free using Midazolam and Fentanyl infusions. Neuromuscular blockade should be considered in all patients with agitation and also at the time of tracheal suctioning. This allows a more precise control of ventilation, pH and $PaCO_2$ and prevents swings in the alveolar pressures caused by

Flow chart 58.4: Pulmonary hypertensive crises

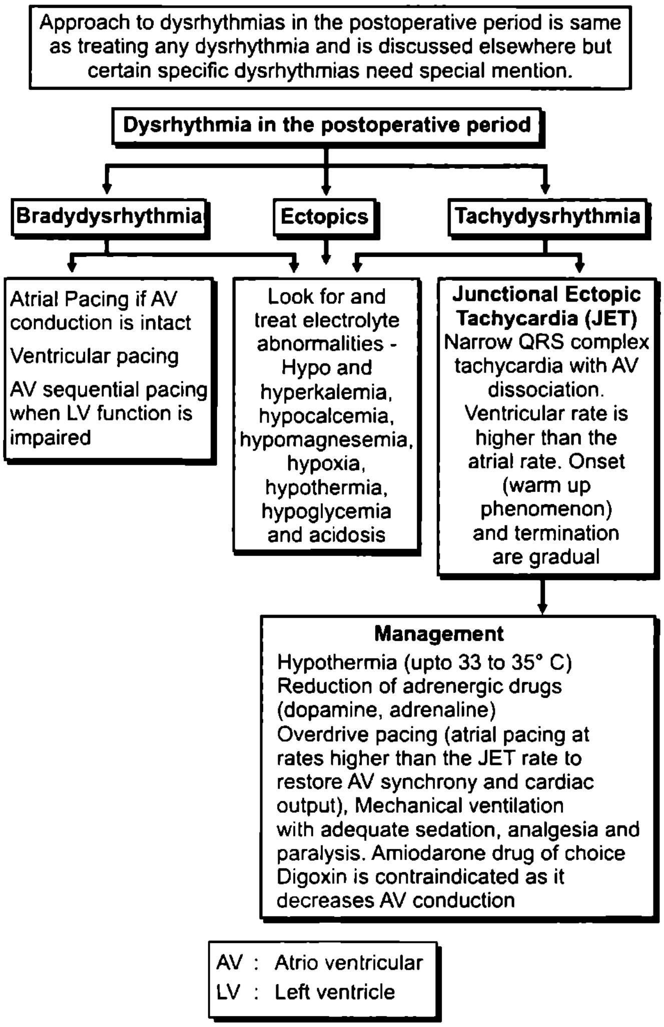

Diagnosis
Severe hypoxemia, decreased cardiac output leading to hypotension and bradycardia
Physiology
In infants less than 3 months, pulmonary vasculature is hyper-reactive. Any precipitating factor leads to severe pulmonary hypertension, increased RV afterload and marked RV dysfunction. Pulmonary hypertensive crisis leads to sudden decrease in the pulmonary blood flow, marked hypoxemia, metabolic acidosis and further reduction in the RV cardiac output.
Precipitating Factors
Hypoxia, hypercarbia, acidosis, hypothermia, hyperthermia, hypoglycemia, pain and tracheal stimulation due to suctioning
Treatment
Decrease RV afterload (Treat the precipitating factors)
Correct Hypoxia
Increase FiO_2
Correct Hypercarbia
Increase ventilatory rate
Increase tidal volume
Decrease I-time
Decrease RV afterload
Decrease PEEP
Decrease mean airway pressure
Correct Acidosis
Bicarbonate administration
Treat pain
Analgesia
Sedation
Paralysis
Correct temperatures
Treat hypoglycemia
Pharmacological Management
Milrinone
Nitric oxide
Increase preload (fluids)
No improvement
High Frequency Ventilation
No improvement
ECMO
RV : Right ventricle
PEEP : Positive end expiratory pressure
ECMO : Extra corporeal membrane oxygenation

coughing and straining. One of the most successful approaches to reducing the pulmonary artery pressures is manipulation of the cardiorespiratory interactions to lower pulmonary vascular resistance. Therapy consists of increasing PaO_2, increasing pH, decreasing $PaCO_2$, and minimizing intrathoracic pressures. Increasing pH reduces PVR. An increase in both the alveolar and arterial O_2 by increasing FiO_2 will result in reduction in PVR. Mechanical ventilation is usually required in patients with pulmonary artery hypertension. Patients benefit from hyperventilation but mean airway pressures should be limited because high mean airway pressures will increase PVR. PEEP should be manipulated judiciously as low PEEP would lead to collapse of the alveoli and high PEEP would cause alveolar overdistension and compression of the pulmonary capillaries and increased PVR. Other methods aimed at lowering the pulmonary artery pressures and improving RV function includes optimizing preload and contractility. Because of increased afterload, the RV requires higher than usual filling pressures to maximize RV stroke volume. Pharmacologic agents that have helped in increasing RV contractility as well as decreasing RV afterload include phosphodiesterase inhibitors especially milrinone. Nitric oxide, an endothelium derived relaxing factor, has been the most promising and is a selective pulmonary vasodilator.[24]

Dysrhythmias (Flow chart 58.5): Children with congenital heart disease are predisposed to atrial and ventricular dysrhythmias both before and after surgical repair.[25, 26] In general atrial surgery increases the risk of sinus node dysfunction and atrial dysrhythmias, and ventricular surgery is associated with ventricular tachydysrhythmias. Certain anomalies have predisposition to certain dysrhythmias, e.g. Ebstein's anomaly is associated with WPW syndrome in 10% patients.[27] Ventricular dysrhythmias are seen in children with aortic valvular disease because of ventricular hypertrophy, increased ventricular wall stress and myocardial oxygen demand. The site of surgical repair also gives a clue to the type of arrhythmia that may occur in the postoperative period, e.g. surgery for VSD either isolated or associated with other cardiac defects like Fallot's Tetrology or Transposition of great arteries predisposes the risk of Junctional ectopic tachycardia or varying degrees of AV block, AV canal defects are more predisposed to varying degrees of A-V block.[28] Postoperatively electrolyte abnormalities (Hypo and hyperkalemia, hypocalcemia), hypoxia, hypothermia, hypoglycemia and acidosis may cause ventricular ectopics and tachyarrhythmias. Although prolongation of QT_c by inhalational anesthetics (enflurane, isoflurane) is commonly seen, ventricular arrhythmias related to QT prolongation are rare.[29]

The therapy of cardiac dysrhythmias in the post-operative settings is effective if dysrhythmias are anticipated. It is beyond the scope of this chapter to go into the details of each dysrhythmia and its management but the basic principles in management of post-operative cardiac dysrhythmias needs mention. For life threatening tachydysrhythmias

Flow chart 58.5: Dysrhythmias



Approach to dysrhythmias in the postoperative period is same as treating any dysrhythmia and is discussed elsewhere but certain specific dysrhythmias need special mention.

Dysrhythmia in the postoperative period

Bradydysrhythmia

Atrial Pacing if AV conduction is intact

Ventricular pacing

AV sequential pacing when LV function is impaired

Ectopics

Look for and treat electrolyte abnormalities - Hypo and hyperkalemia, hypocalcemia, hypomagnesemia, hypoxia, hypothermia, hypoglycemia and acidosis

Tachydysrhythmia

Junctional Ectopic Tachycardia (JET)
Narrow QRS complex tachycardia with AV dissociation. Ventricular rate is higher than the atrial rate. Onset (warm up phenomenon) and termination are gradual

Management

Hypothermia (upto 33 to 35° C)
Reduction of adrenergic drugs (dopamine, adrenaline)
Overdrive pacing (atrial pacing at rates higher than the JET rate to restore AV synchrony and cardiac output), Mechanical ventilation with adequate sedation, analgesia and paralysis. Amiodarone drug of choice
Digoxin is contraindicated as it decreases AV conduction

AV : Atrio ventricular
LV : Left ventricle

when the patient demonstrates acute hemodynamic instability, pharmacotherapy takes a second place to emergent cardioversion. Adequate oxygenation, correction of electrolyte disturbances and adequate sedation are important baseline therapeutic endeavors for all tachydysrhythmias. Another factor in treating tachydysrhythmias is the drugs the patient is receiving particularly dopamine and epinephrine and digoxin. Lidocaine is the antiarrhythmics of choice for ventricular tachycardia (1 mg/kg bolus followed by 20-50 ug/kg/min). For refractory tachydysrhythmias amiodarone is the drug most commonly used. Bradycardia in ICU is not defined by specific heart rates. Instead bradycardia is any slow rate associated with hypoperfusion, hypotension or CHF. The underlying dysrhythmia may be sinus bradycardia, or varying degrees of AV block. If patient is hemodynamically unstable immediate measures to improve the heart rate include drugs like epinephrine, atropine (0.01 mg/kg iv bolus) or isoproterenol and temporary pacing (atrial pacing if AV conduction is intact, ventricular pacing, AV sequential pacing if ventricular function impaired). All sedatives and medications aggravating bradycardia must be stopped. In case of use of digoxin, it should be withheld.[30]

Junctional ectopic tachycardia (JET) needs special mention as it is a serious postoperative rhythm disturbance associated with poor hemodynamic performance and poor recovery in the postoperative period. It results from a site of abnormal automaticity within the AV node of bundle of His. It is a narrow QRS complex tachycardia with AV dissociation. In this tachycardia the ventricular rate is higher than the atrial rate. The onset (warm up phenomenon) and termination are gradual. Ventricular rates range from 160 – 250 beats/min and rates as high as 370 beats/min have been reported. Postoperative JET management includes creating hypothermia (upto 33-35°C), reduction of adrenergic drugs (dopamine, adrenaline) and overdrive pacing (atrial pacing at rates higher than the JET rate to restore AV synchrony and cardiac output), mechanically ventilating the patient with adequate sedation, analgesia and paralysis. If the measures are unsuccessful, amiodarone is the drug of choice though not without side effects. Digoxin is contraindicated in JET and should never be used for ever in a patient with history of JET.[31]

Management of Inotropes

Inotropes are drugs used to improve myocardial contractility as well as to manipulate the afterload and thus help in the immediate postoperative period to optimize the cardiac output. In case of low cardiac output due to LV dysfunction cardiac contractility is improved by the combination of dopamine and dobutamine and afterload reduction is achieved by dobutamine and milrinone. Usual course is to initiate dopamine and titrate to maintain normal perfusion and/or slightly subnormal blood pressures. If dopamine requirement is increasing beyond 10 – 12 ug/kg/min, Dobutamine is added and titrated to increase myocardial contractility and counter the increased afterload due to dopamine. Most centers now prefer to add milrinone before dobutamine because of inotropy and better afterload reduction. Preload in LV dysfunction is manipulated by ventilatory parameters. For RV dysfunction inotropy is achieved by dopamine/ dobutamine titrated as per requirements and afterload reduction (pulmonary vasodilation) is achieved using nitroglycerine and milrinone.[32] Preload reduction is achieved by the use of diuretics.

Ventilation

A critical factor in cardiac physiology is the understanding of the respiratory physiology as the two systems usually function as a single unit. That is the reason cardiorespiratory physiology is the more appropriate term to describe the interactions between the two systems. In infants and children with heart disease the effects of cardiorespiratory interactions are exaggerated. Therefore in such children the effects of respiratory support on cardiac function are important and needs to be adequately manipulated to get the maximum benefits.[33]

Effects of Ventilation on Heart Rate

Positive pressure ventilation has minimal effects on heart rate. An increase in lung volume results in reflex bradycardia, which is usually not much with normal tidal volumes of 8-10 ml/kg. High tidal volume ventilation upto 15 ml/kg may result in clinically significant bradycardia.

Effects of Ventilation on Right Ventricular Function

The effects of ventilatory maneuvers on right and left ventricular function are markedly different. The right ventricle is extremely sensitive to alterations in the intra thoracic pressures.[34]

- The venous return to the right side of the heart is passive and results due to pressure difference between the systemic venous return and the right atrium. When the right atrial pressure is 0, there is no pressure gradient between the systemic veins and the right atrium and venous return is maximum. When the right atrial pressure increases, pressure gradient between the systemic veins and the right atrium decreases and thus venous return decreases. During normal inspiration the intra thoracic pressure is negative, the right atrial pressure is low and the venous return to the right heart is maximum. During expiration the intrathoracic pressure increases and becomes positive, this increases the right atrial pressure and thus the venous return decreases. During positive pressure ventilation (PPV) and use of PEEP, the intrathoracic pressure is always high, it increases the right atrial pressure and thus decreases the venous return to the right heart. Thus PPV and PEEP decrease the RV performance by decreasing the RV preload.
- Another important factor in ventricular contractility is the myocardial oxygen delivery. In a normal RV the coronary blood flow occurs in the systole and depends on the pressure difference between the aorta and the RV. During PPV, the RV pressure increases, this decreases the pressure gradient between the aorta and the RV, thus decreasing the RV coronary blood flow. As a result the RV contractility, cardiac output and the oxygen delivery decreases. Now theoretically the logic seems good but normally the pressure difference between aorta and RV is such that minor variations in intrathoracic pressures do not alter the RV coronary blood flow. This concept becomes important in certain pathophysiologic states where the aortic pressure is low or there is RV dysfunction which are usually seen after CPB. Here the intrathoracic pressure changes become clinically significant and ventilatory adjustments can be done to optimize the venous return and the RV contractility.
- The increased intrathoracic pressures also alter the pulmonary vascular resistance to which the RV is extremely sensitive (RV afterload). Manipulation of the pulmonary mechanics to alter the RV afterload is an important therapeutic option in postoperative RV dysfunction, especially in infants and children. At low lung volumes the hypoxic pulmonary vasoconstriction occurs and the large and medium sized blood vessels have a tortuous course thus increasing the pulmonary vascular resistance. As lung volumes increase, hypoxia improves, pulmonary vasodilatation occurs and the pulmonary vessels become more linear thus decreasing the pulmonary vascular resistance. At still higher lung volumes hyper expansion of the alveoli occurs which leads to the compression of the alveolar capillaries thus increasing the vascular resistance. Thus PVR is high at very low and very high lung volumes and is lowest at FRC. Thus ventilatory adjustments in terms of tidal volumes and PEEP can be used to alter the RV afterload.[34]

Effects of Ventilation on Left Ventricular Function

The effects of ventilatory manipulations on LV function are more beneficial but less well understood.

- Based on the similar concept as that of RV, ideally increased intrathoracic pressures should decrease the venous return to the left heart. But here the concept usually works the other way round. Unlike the RV, the LV derives its preload from intra thoracic sources. Increase in the intra thoracic pressures result in increase in pulmonary vascular pressures and more blood is pumped into the left side of the heart thus improving the venous return to the LV.
- LV contractility is generally not altered by ventilatory manipulations. However markedly increased intrathoracic pressures may result in decreased myocardial contractility. Increased airway pressures reduce the LV preload and alter the afterload thus resulting in low cardiac output, decreased myocardial oxygen delivery and contractility.

- LV afterload is reduced by ventilatory manipulations by several complex interactions. The end result of a persistent increase in intra thoracic pressure is a decrease in the LV wall tension as a result of aortic pressure autoregulation.[35]

Ventilatory Settings

The major goal of respiratory support is to optimize the oxygen delivery to the tissues by improving the oxygen content of the blood and decreasing the oxygen needs of the respiratory muscles by decreasing the work of breathing.

- **Initial ventilatory settings** would depend on the settings required intraoperatively and later on finer adjustments can be made according to the cardiac physiology to optimize the cardiac output.
- Start with a FiO_2 of 1.0. Once the transport from the operating room is done and hemodynamics stabilized, FiO_2 can be decreased upto 0.5 based on the ABG analysis and maintaining the saturations around 90-95%. Arterial hypoxemia should not be tolerated, FiO_2 can be increased but the cause needs to be ascertained.
- **Ventilatory mode** is dependent on the age and weight of the patient. In infants and children less than 10 kg, pressure control mode is the usually preferred mode where as in older children volume control mode in preferred. However with the new generation ventilators, either mode can be used as because volume and pressure measurements are possible in all the modes.
- Start with a **tidal volume** of 8-10 ml/kg. Optimal tidal volume is adjusted according to the chest rise and the underlying cardiac physiology. Low (5 ml/kg) or extremely high tidal volumes (15-20 ml/kg) should be avoided as discussed in the previous section on cardio respiratory interactions.
- **Ventilator frequency** or rate is set based on the normal age related respiratory rates. Hyperventilation if required especially in pulmonary hypertensive crisis can be done by manipulating the tidal volumes. Slight increase or decrease in frequency can be made based on the CO_2 levels on ABG analysis.
- The application of **PEEP** has important implications in the postoperative pediatric cardiac patients. The net effect of PEEP is improved oxygenation. Normal physiological PEEP is 3-4 mm Hg. Variations from the normal would depend on the underlying ventricular function as well as the respiratory status. PEEP is beneficial for LV dysfunction where as it is detrimental for RV dysfunction. In ARDS type of picture PEEP become essential to prevent hypoxia. Initially normal physiological PEEP should be used to recruit the lung volume and to prevent alveolar atelectasis. Later on PEEP can be titrated based on the underlying condition.[36]
- Inspiratory time is usually based on the time constants and manipulations are required in cases of severe hypoxia not responding to manipulations in PEEP or tidal volumes. An inspiratory time of 0.4 – 0.5 sec is usually set for neonates and infants where as 0.5 – 0.7 sec is usually used for older children. In adults the inspiratory times upto 1 sec can be used comfortably.
- Specific ventilatory adjustments are being discussed with specific physiological conditions.
- Weaning from positive pressure ventilation depends on a variety of factors, most important being adequate cardiovascular function and favorable pulmonary mechanics. The most important concept in pediatric cardiac patient is that weaning and extubation are accomplished first followed by manipulation and tapering of the inotropes. Weaning strategies are similar to general pediatric intensive care and involve stepwise reduction in ventilatory parameters. Synchronized intermittent mandatory ventilation (SIMV) + Pressure Support (PS) is the usual mode of weaning. Once an SIMV rate of 8-10 and a pressure support level of 8-10 is reached along with PEEP of 3-4, patient can be shifted on to complete spontaneous respiration (CPAP + PS) and if tolerating well can be planned for extubation.[37]

Sedation, Analgesia and Paralysis

The principles of sedation, analgesia and paralysis in cardiac intensive care are same as that to general pediatric intensive care. However one needs to understand the effects of these agents on the cardiovascular physiology as they become more pronounced in patients with congenital cardiac lesions especially in the postoperative period.

Much attention has been paid to the importance of blunting postoperative stress response after cardiac surgery especially in infants. Neonates undergoing cardiac surgery appear to have more severe and prolonged hormonal metabolic response than adults. Plasma catecholamine levels, glucose, gluconeogenic substrates and lactic acid are recognized as measures of neonatal stress response. Reduction in the metabolic and hormonal stress responses with adequate sedation, analgesia and paralysis has shown to reduce the postoperative morbidity and mortality.[38, 39] We will discuss specific drugs used for sedation, analgesia and paralysis, focusing on their effects on cardiovascular physiology.

Morphine is the prototypic opioid and remains the gold standard analgesic against which all other opioids are compared.[40] It is used both intra-operatively as well as postoperatively for sedation as well as anesthesia. A loading dose of 100 ug/kg followed by continuous infusion of upto 100 ug/kg/hr are used to maintain adequate sedation and analgesia. Postoperative monitoring for pain or awake state includes sudden onset tachycardia or hypertension, patient movement or fall in blood pressure especially in pulmonary hypertensive crisis. In such cases an extra dose of 100 µg/kg can be used to control the pain. Morphine produces peripheral vasodilatation and venous pooling, hence it can cause significant hypotension in hypovolemic patients. However it has minimal hemodynamic effects in euvolemic patients. Morphine may also cause vasodilatation and bronchospasm because of its histamine releasing effects. Morphine inhibits intestinal smooth muscle motility and increases the tone of pyloric sphincter and ileo-ceacal valve. This may be particularly important postoperatively as it may delay initiating feeds due to decreased bowel sounds. In our unit, we usually decrease the morphine infusion to about 10-20 ug/kg/hr by day 2 once it's comfortable to add oral analgesics. This helps in initiating feeds as well as tolerance of feeds.[41]

Fentanyl is 100 times more potent than morphine and is devoid of sedative or hypnotic activity. It is used in a dose of 1-3 ug/kg loading followed by 1-5 ug/kg/hr. When used as a component of cardiac anesthesia, doses of 50-100 ug/kg are administered. Fentanyl blocks nociceptive stimuli with concomitant hemodynamic stability and thus is the drug of choice for cardiac patients. It blocks the systemic and pulmonary hemodynamic responses to pain besides preventing the metabolic and endocrine stress response to pain. The most important side effect of Fentanyl is chest wall rigidity after rapid infusions of 5 ug/kg or more. So Fentanyl should never be pushed as a bolus and infusions upto 5 ug/kg/hr should be monitored closely. In case of chest wall rigidity, muscle relaxants need to be used.[42]

Benzodiazepines constitute a family of drugs that are sedative, hypnotic and anxiolytic and have anticonvulsant properties. Midazolam is the most commonly used benzodiazepine these days. It is water soluble, four times more potent than diazepam and is well absorbed via i/m, oral, rectal or nasal routes. Benzodiazepines decrease both preload and afterload, so in the presence of hypovolemia can cause significant hypotension. They significantly affect blood pressure and cardiac output when combined with opioids, so great caution must be used while combining these two classes of drugs. Midazolam is used as intermittent boluses postoperatively if the desired effect is not achieved with morphine or sometimes also as continuous infusion of 0.05-0.2 mg/kg/hr.[43]

Muscle relaxants are also an important group of drugs for the cardiac intensivist in the post-operative period. It must be remembered that this class of drugs is used as adjunct to and not substitute for, analgesics/ sedatives. It is important that the patient must be adequately sedated and pain free along with the use of muscle relaxants because with paralysis most of the physical signs of pain are masked and one has to rely only on hemodynamic variables, which may be disturbed because of the cardiac condition itself. Initially paralyzing agents were used as continuous infusions but the neuro muscular blocking effects were markedly prolonged which would delay weaning from ventilation and initiated various forms of neuro-myopathies. Current recommendations suggest intermittent boluses as this allows the intensivist to see the recovery from paralysis before giving the next dose if required.[44]

Pancuronium is the most frequently used long acting muscle relaxant in the operating room and ICU. It is used in a dose of 0.1 – 0.15 mg/ kg, for intubation and postoperatively. The effect lasts for about 1 hour and excretion is through kidneys. As such the risk of accumulation is increased in renal failure.[45, 46] In such patients Vecuronium or atracurium are the muscle relaxants of choice. Another important factor in cardiac physiology is that this drug causes tachycardia without noticeable effects on blood pressure, which may sometimes not be acceptable in postoperative cardiac patient. Vecuronium is a derivative of pancuronium and differs from it – duration of action is less, does not cause tachycardia and is primarily dependent on biliary excretion. Atracurium is an intermediate acting muscle relaxant and is unique in that it is metabolized non-enzymatically by Hoffmann degradation. It does not depend on renal or hepatic elimination and there is no accumulation. Hence it is an important muscle relaxant in post-operative cardiac patient – both as intermittent boluses or continuous infusions. Half-life is small and there is no accumulation.[47]

Ketamine and propofol are newer anesthetic agents who have gained popularity in pediatric cardiology and cardiac surgery, more so in procedures like cardiac catheterization. Ketamine was first used in pediatric cardiac surgery in 1973 and found to be well tolerated even in the sickest of the patients. In induction of anesthesia, the mean blood pressures were found to be more stable with ketamine than halothane/nitrousoxide – oxygen mixture. Some studies have shown that ketamine increases pulmonary artery pressures so its use is restricted in patients known to have pulmonary hypertension or pulmonary vascular reactivity.[48] In patients undergoing cardiac catheterization to determine operability based on pulmonary vascular pressures or reactivity, ketamine should be avoided. In such cases propofol would be a better anesthetic of choice.[49]

Fluids and Electrolytes

Fluids and electrolyte management in post-operative period is based on the stress response to surgery. The fluids are restricted initially because of sodium and water retention. Fluids are calculated on the basis of Holiday and Segar formula based on the body weight i.e. < 10 kg – 100 ml/kg, 10-20 kg – 1000 ml + 50 ml/kg for each kg above 10 kg and > 20 kg – 1500 ml + 20 ml/ kg for each kg above 20 kg. Fluids are restricted to 25% of maintenance fluids on day 1, 50% on day 2 and then increased by 10% on subsequent days till 100% maintenance fluids are reached. Any fall in blood pressures or decreased perfusion are dealt with small boluses as and when required. The fluid on day 1 and 2 is usually 5% or 10% dextrose and sodium is added to the fluid by day 3. Potassium is added to fluids based on the serum potassium levels and urine output. Fluid boluses used are usually blood products – packed red cell and plasma, 5% albumin saline and normal saline. Fluid boluses used in postoperative cardiac patients should be small (1-2 ml/kg, maximum 5 ml/ kg) and titrated to effect based on the cardiac performance. In case of pulmonary and systemic edema, fluid restriction is maintained, combined with furosemide infusions and peritoneal dialysis if renal function is impaired. Management of hypo or hypernatremia and hypo or hyperkalemia is same as being followed in general pediatric intensive care.[50]

Calcium homeostasis is important in a post-operative cardiac patient as calcium acts both on the heart (inotropy) and peripheral vasculature (increases vascular tone). Calcium homeostasis is disturbed by cardiopulmonary bypass as well as use of blood products especially in neonates.[51] Ionized calcium is more important and levels should be maintained within the range of 0.9 – 1.3 mmol/lit. Calcium replacement is given as calcium gluconate 10% in a dose of 30 mg/kg (90.3 ml/kg) as iv bolus or as infusion of 30 – 100 mg/kg/hr (0.3 – 1 ml/kg/ hr). This requires frequent measurements of ionized calcium, which is usually present in the arterial blood gas analysis. Important points to consider are to give calcium through a central line, not to combine with soda bicarbonate and bradycardia can result from rapid administration.

Nutrition

Nutrition is very important in pediatric cardia patients more so that these patients have increase metabolic requirements because of their cardia condition.[52] The management goal is to provid adequate calories to replenish the pre-existin nutritional deficit, the deficit as a result of surgica stress and to support the reparative process in the post-operative period.

In the postoperative period enteral feeds are initiated after hemodynamic stability has been achieved, usually by postoperative day 1 or 2. In neonates, particularly with a stormy course and anticipated delay in enteral feeding, parenteral nutrition is initiated on day 1. Once hemodynamic stability is achieved, trophic feeds are initiated as early as possible. The trans-pyloric route of enteral feeding has been advocated as the preferential route in critically ill patients, advantages being able to deliver greater quantities of calories, to overcome delayed gastric emptying and to minimize the risk of aspiration associated with reflux. Trans-pyloric feeding is known to be complicated by gastric bleeding, bacterial overgrowth, increased stool frequency and steatorrhea.[53]

Renal Issues

The renal issues are important in a cardiac patient because of two reasons – one the renal function may be impaired preoperatively because of low cardiac output and decreased renal perfusion and second, because of the effects of cardiopulmonary bypass as discussed earlier.[54] The details of renal injury mechanisms are beyond the scope of this chapter. Post-operatively renal failure management needs to be aggressive for a better outcome. Management issues include, increasing renal perfusion, fluid restriction, use of loop diuretics, correction of hyperkalemia and metabolic acidosis. Early institution of peritoneal dialysis is important especially in neonates to remove excess fluids and correction of azotemia and hyperkalemia. This is because neonates with postoperative impaired myocardial function and renal failure may not tolerate the degree of hypervolemia and hyperkalemia. That is the reason neonates undergoing open heart surgery are brought out post-operatively with peritoneal catheter in situ.[55] Once the polyuric phase starts, the goals of management are to maintain fluid and electrolyte balance and prevention of further renal injury by dehydration.

Coagulation Issues

Cardiopulmonary bypass alters the coagulation system through factor and platelet hemodilution and platelet dysfunction due to activation and hypothermia.[56,57] These abnormalities are greatly exaggerated in infants and neonates as compared to adults. The differentiation between medical and surgical bleeding is important. Blood loss in excess of 10% of the total circulating volume in any hour, or blood loss greater than 5% of the patient's total circulating volume for more than 3 consecutive hours, requires surgical exploration. Patients after cardiopulmonary bypass are screened for PT and APTT, activated clotting time and platelets. Because of the use of heparin during cardiopulmonary bypass, rebound heparin effect may be seen in the immediate postoperative period requiring use of protamine sulphate. Usually 1 – 1.3 mg of protamine is required for every 100 units of heparin used during bypass. Protamine dose requirements are more in neonates as compared to older infants and children. This is because heparin effect is more pronounced in neonates because of their reduced metabolic capability and exposure to hypothermia.[58] Half of the total calculated dose is used in the operation theatre immediately after bypass. Rest of the dose is titrated and administered in the ICU post-operatively based on the activated clotting time results. Side effects of protamine include hypotension, pulmonary vasoconstriction and anaphylactic reactions. Excess protamine may itself result in bleeding.

Component therapy begins with platelets since both qualitative and quantitative platelet dysfunction is the hallmark of post-cardiopulmonary bypass bleeding.[59] Platelet transfusion is warranted in the setting of thrombocytopenia and prolongation of the bleeding time with significant bleeding. Fresh frozen plasma (FFP) is used to replenish factor deficiencies. Packed red cell transfusions are warranted in case of excessive bleeding and cryoprecipitate for replenishing fibrinogen.[60] The usual approach is to transfuse packed cells and FFP initially as guided by the hematocrit levels and amount of bleeding. Platelets are transfused at a dose of one unit for every 10 kg. If significant bleeding persists despite adequate replacement of FFP and platelets, cryoprecipitate is transfused in a dose of one unit for every 10 kg.

There is growing literature on the use of pharmacological agents to reduce bleeding and restore hemostasis after cardiopulmonary bypass. Epsilon amino caproic acid (EACA), by inhibition of fibrinolysis, has shown to produce a significant reduction in blood loss. It is used in a dose of 100 – 150 mg/kg loading followed by continuous infusion of 10-15 mg/kg/hr.[61] Cyanotic children whose bypass time exceeds 60 minutes have shown the greatest benefit. Aprotinin, a serine protease inhibitor, inactivates various enzymes involved in coagulation. It has been shown to dramatically reduce blood loss in adults after cardiopulmonary bypass but results in children have been variable.[62] Aprotinin is a heterologous protein and side effects include allergic and anaphylactic reactions.

Important management points in specific cardiac lesions

For the purpose of convenience, specific cardiac lesions are discussed based on broad categories of acyanotic and cyanotic heart defects. In acyanotic heart defects, left to right shunts and obstructive lesions are covered, and in cyanotic heart defects, lesions discussed are right to left shunts with decreased pulmonary blood flow, right to left shuts with increased pulmonary blood flow and single ventricle complexes. The basic principles of intensive care management remain same and specific points in the management will be discussed in this section.

Acyanotic Heart Defects (Flow chart 58.6)

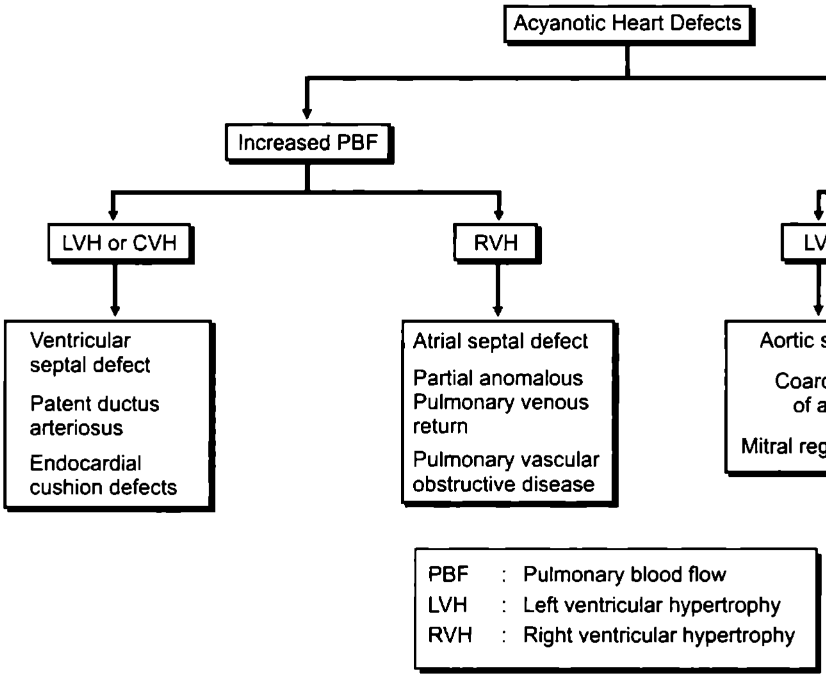
Left to Right Shunts

These include atrial septal defects, ventricular septal defects, patent ductus arteriorus and atrio-ventricular canal defects. In these lesions Qp: Qs ratio is increased and patients are managed for congestive heart failure in the pre operative period. Postoperative period requires continuation of the decongestive management (diuretics for preload reduction, ACE inhibitors for afterload reduction and inotropes for myocardial contractility)

ASD: Most ASDs have a stable postoperative period and are extubated early. Low cardiac output may be seen, mostly due to hypovolemia due to fluid shifts because of cardiopulmonary bypass. Atrial arrhythmias may develop which are usually responsive to digitalization. Inotropes are rarely required in these children except in older patients who have elevated pulmonary vascular resistance due to increased pulmonary blood flow[63] (Figure 58.1).

VSD: Most VSDs are repaired via the transatrial approach thus avoiding the deleterious effects of ventriculotomy. Ventricular dysfunction depends on

Flow chart 58.6: Approach to acyanotic heart defects


Acyanotic Heart Defects
Increased PBF
Normal PBF
LVH or CVH
RVH
LVH
RVH
Ventricular septal defect
Patent ductus arteriosus
Endocardial cushion defects
Atrial septal defect
Partial anomalous Pulmonary venous return
Pulmonary vascular obstructive disease
Aortic stenosis
Coarctation of aorta
Mitral regurgitation
Pulmonary stenosis
Coarctation of aorta in infants
Mitral stenosis
PBF : Pulmonary blood flow
LVH : Left ventricular hypertrophy
RVH : Right ventricular hypertrophy

the degree of preoperative heart failure and cardiopulmonary bypass. Low cardiac output is seen commonly in the postoperative period requiring inotropic support.[64] Perimembranous VSD's are close to the AV node and repair may lead to various types of arrhythmias and heart blocks. Junctional ectopic tachycardia is the commonest arrhythmia and needs urgent management.[65] Other common arrhythmia is supraventricular tachycardia which is usually managed with digitalis. Heart block occurs due to excessive traction of the tricuspid annulus or edema associated with sutures placed near the conduction tissue. Heart block may be of various degrees and transient or permanent. It is initially managed with overdrive pacing and if it persists beyond 7-10 days postoperatively it is usually permanent and requires permanent pacemaker insertion.[66] With early repairs of VSD especially in infancy and that too in the first 6 months of age, pulmonary hypertension is seen commonly and should be aggressively managed (Figure 58.2).

AV Canal defects: AV canal defects are endocardial cushion defects, may be partial or complete and are usually associated with other cardiac defects.[67] Partial AV canal defects are also known as Ostium primum ASDs. Both types are associated with abnormal mitral valve. In partial AV canal defects, the severity of lesion is determined by the degree of mitral insufficiency. Complete AV canal defects have shunting that occurs at systemic pressures and lead to RV and pulmonary artery pressures equalizing systemic pressures. As such pulmonary vascular resistance rises and becomes fixed and permanent in the first month of life. Thus this defect requires early closure before the onset of pulmonary hypertension and inoperability (Figure 58.3).

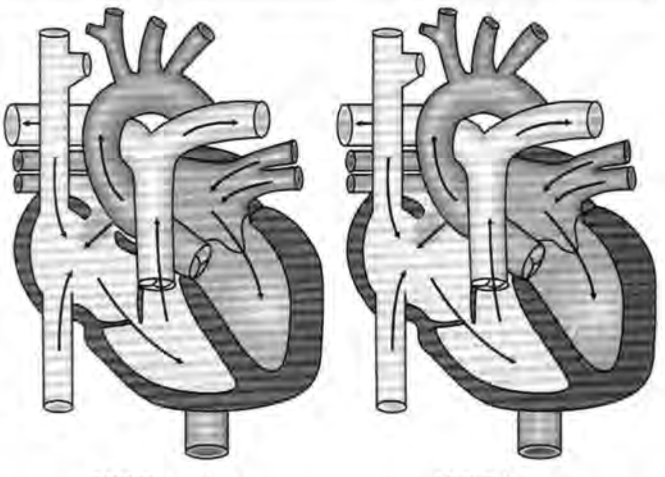

ASD Secundum ASD Primum

Fig. 58.1: VSD

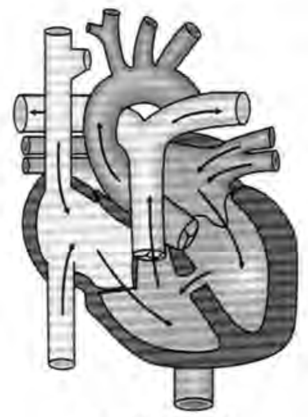


Fig. 58.2: VSD

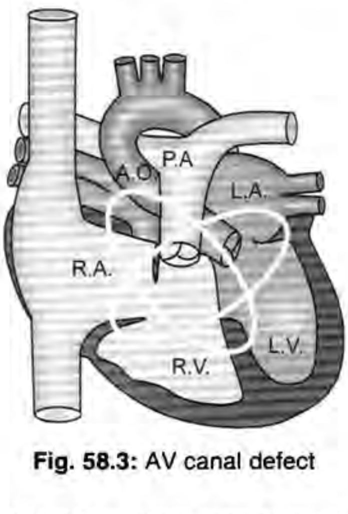


Fig. 58.3: AV canal defect

The major postoperative issues remain same in both types of AV canal defects and include the degree of mitral insufficiency, pulmonary hypertension, low cardiac output requiring inotropic support and dysrhythmias associated with the degree of atrial dilatation.[68] The major difference is the severity of the complications in complete AV canal defects. Because of the proximity of the AV node to the area of surgical repair, varying degrees of heart blocks may occur requiring AV sequential pacing. There is also risk of development of Junctional ectopic tachycardia. Low cardiac output persisting beyond 48-72 hrs requires evaluation of RV and LV function, presence of residual defects and LV outflow tract obstruction. LV outflow tract obstruction if present would require surgical intervention.[69]

Obstructive lesions: These include varying degrees of left ventricular outflow obstruction from coarctation of aorta to various types of interrupted aortic arch. Most of the critical lesions have duct dependent circulation to the lower half of the body and need intensive preoperative management in case of ductal closure. Most of these babies are sick preoperatively and present with upper body hypertension and signs of decreased perfusion to lower half of the body – renal failure, gut ischemia.[70]

Coarctation of aorta: The postoperative complications depend on the degree of preoperative insult and on the aortic cross clamp time. Pre-operative necrotizing enterocolitis and renal failure are an important cause of concern postoperatively. Other important postoperative complication is paraplegia which is related to the prolonged aortic cross clamp time.[71] This requires removal of sedation and paralysis early to assess for neurological complications. The surgery for coarctation of aorta is mostly done through left thoracotomy, so complications of thoracotomy need to be assessed – phrenic nerve injury leading to diaphragmatic paralysis, injury to recurrent laryngeal nerve causing stridor, thoracic duct injury leading to chylothorax. Diaphragmatic paralysis may be evident by elevated hemi diaphragm and difficulty in weaning from ventilator, but mostly seen post extubation. Stridor is usually evident after extubation. Chylothorax usually requires chest tube insertion, keeping the child nil by mouth and initiating parenteral nutrition. Use of octreotide has gained popularity in recent times but cases not getting controlled require reoperation and thoracic duct ligation[72] (Figure 58.4).

The incidence of hypertension is more in patients repaired later in life. In the initial postoperative period systemic hypertension[73] requires antihypertensive management with sodium nitroprusside. The cause of this hypertension is hyperreninemia due to decreased blood supply to the kidneys though renal functions are usually normal. Post repair of the coarctation the blood supply to the kidneys improve but renin levels take 7-10 days time to settle down. Other cause of post surgical hypertension is the surgical stimulation of sympathetic nerve fibers located in the aortic isthmus, which leads to release of norepinephrine and rise in blood pressure. In long standing hypertension after coarctation repair, baroreceptors have been reset to a higher baseline pressure.[74]

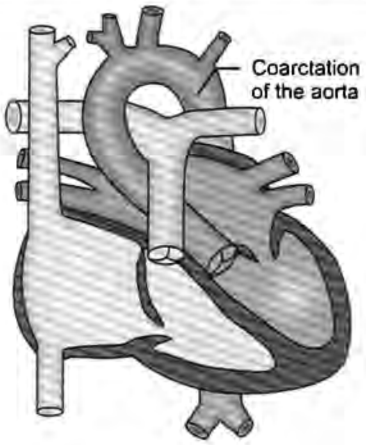


Fig. 58.4: Coarctation of aorta

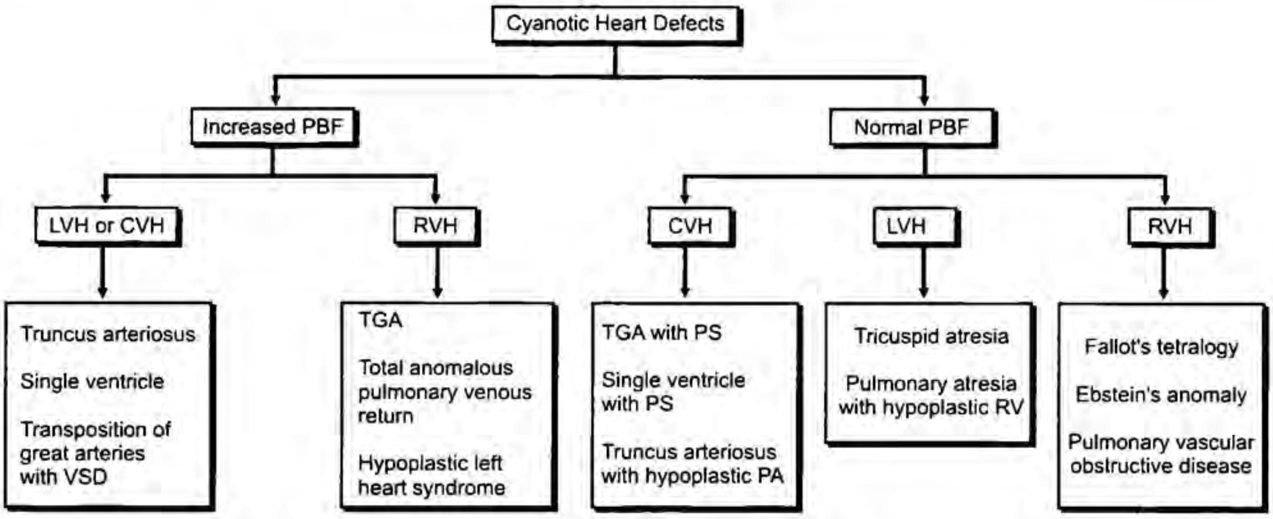
Postcoarctectomy syndrome is a well described complication after coarctation repair. The patient presents with severe abdominal pain, associated with hypertension, fever, abdominal tenderness, vomiting, melena and leukocytosis. It occurs approximately 48 hrs after surgery and results from sudden increase in blood pressure to vessels below coarctation. This results in necrotizing arteritis of the mesenteric vessels. The changes are reversible and the treatment or prevention is by control of hypertension.[75]

Cyanotic Heart Defects (Flow chart 58.7)

Right to left shunts: This is a diverse group of cardiac lesions and going into the details of every lesion is beyond the scope of this chapter. However common lesions are being discussed. In right to left shunt with decreased pulmonary blood flow, Tetrology of Fallot and Ebstein's anomaly are being discussed. In right to left shunt with increased pulmonary blood flow, Transposition of great arteries and Total anomalous pulmonary venous connection are being discussed.

Tetrology of fallot (TOF): This is one of the most common congenital cardiac anomalies with an

Flow chart 58.7: Approach to cyanotic heart defects


Cyanotic Heart Defects
Increased PBF
Normal PBF
LVH or CVH
RVH
CVH
LVH
RVH
Truncus arteriosus
Single ventricle
Transposition of great arteries with VSD
TGA
Total anomalous pulmonary venous return
Hypoplastic left heart syndrome
TGA with PS
Single ventricle with PS
Truncus arteriosus with hypoplastic PA
Tricuspid atresia
Pulmonary atresia with hypoplastic RV
Fallot's tetralogy
Ebstein's anomaly
Pulmonary vascular obstructive disease

PBF : Pulmonary blood flow
LVH : Left ventricular hypertrophy
CVH : Combined ventricular hypertrophy
TGA : Transposition of great arteries
PS : Pulmonary stenosis
RVH : Right ventricular hypertrophy
VSD : Ventricular septal defect

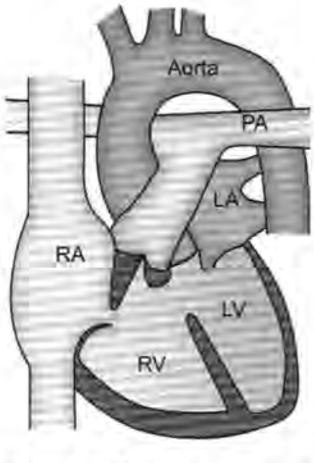

Aorta
PA
LA
RA
LV
RV

Fig. 58.5: Tetrology of Fallot

incidence of 3-6 per 10000 births.[76] Patients with TOF usually go in for complete correction early unless it is precluded by risk factors that necessitate palliative procedures like BT shunt, Pott's shunt or Waterston shunt (Figure 58.5).

For a palliative procedure, usually done through a lateral thoracotomy, important issues relate to the complications of thoracotomy discussed earlier, i.e. injury to phrenic nerve, recurrent laryngeal nerve or thoracic duct. For BT shunt intensive care management include maintenance of intravascular volume and anticoagulation to prevent shunt block. For this once the bleeding has stopped, patient is initiated on intravenous heparin at a rate of 10 units/kg/hour. Once the patient is extubated and on feeds, oral aspirin is added and heparin is stopped 24 hrs later. The size of the shunt is extremely important and influences the postoperative course. In case of a small shunt, oxygenation may not be adequate and saturations may remain low. If the shunt is too large it will lead to pulmonary flooding at the cost of steal of blood from the systemic circulation. Such patients land up into shock and multiorgan failure because of decreased systemic circulation and pulmonary edema like picture because of increased pulmonary circulation.[77]

The complete repair is usually done through transatrial approach under cardiopulmonary bypass. Commonest postoperative issue is low cardiac output requiring inotropic support.[78] Patients with TOF have right ventricular hypertrophy and smaller RV volumes. As such these patients can increase their cardiac output more effectively by increasing their heart rate rather than the stroke volume. These patients thus benefit from atrial pacing along with inotropes. These patients have poor RV compliance so they need higher central venous pressure (usually around 10-12 cm of H_2O) to maintain the cardiac output. Low cardiac output may also be due to RV or LV dysfunction *per se* because of cardiopulmonary bypass. The complications related to the site of VSD repair have been discussed under VSD and include junctional ectopic tachycardia and heart blocks. The relief of RV outflow tract obstruction either by transannular patch or repair of the valve results in pulmonary insufficiency but because of RV hypertrophy is usually well tolerated. One also needs to look at the presence of residual defects because they may prolong the postoperative course. Ventricular tachydysrhythmias occur in 0.3 – 3% of patients after complete repair and have not been related to the success of the repair.[79]

Transposition of great arteries (TGA): TGA comprises about 7 -8% of all congenital heart defects. 75% of TGA patients have isolated ventriculo – arterial discordance with patent foramen ovale or PDA.[80] This condition presents with cyanosis and increased pulmonary blood flow. VSD is present in 20% of patients of TGA and allow adequate mixing. Left ventricular outflow tract obstruction (LVOTO), i.e. decreased pulmonary blood flow is present in 20% of patients of TGA with VSD. CoA is present in about 10% of patients of TGA with VSD. TGA with intact ventricular septum (IVS) is usually duct dependent because patent foramen ovale is insufficient for adequate mixing. This subset of patients presents at the time of ductal closure and are usually very sick. In such patients, ductal opening is tried with prostaglandin E_1 and urgent balloon atrial septostomy is the procedure of choice. Surgical correction (arterial switch operation) is usually undertaken after stabilizing the patient in the ICU. Another important point is the variation in coronary anatomy, especially intramural coronaries because it has implications on the surgical procedure. The need to discuss associated anomalies with TGA is important as this helps to decide the timing of surgery, the type of surgical procedure and the postoperative management. Arterial switch operation (ASO) was first employed in 1975 by Jatene for TGA with VSD and modified by Lacompte in 1981. With the improvement in surgical technique and advances in cardiopulmonary bypass the success rate for this surgery has dramatically improved. Currently the best centers have mortality of ASO of less than 1%[81] (Figure 58.6).

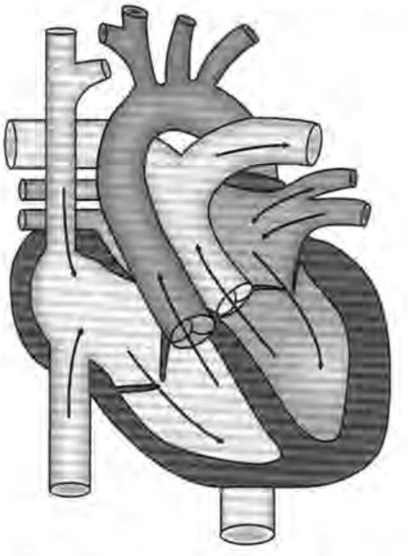


Fig. 58.6: Transposition of great arteries

Ideally ASO should be performed within 2 weeks of age. After ASO the LV, which was pumping against low pulmonary resistance, is acutely placed in a high-pressure circuit and required to support systemic output. The ability of the LV to adapt to the systemic workload takes days to weeks depending upon the timing of surgery. If the surgery is delayed, the LV usually decompensates and LV dysfunction is marked.[82] The aim of postoperative management is to maintain a low pressure, high flow circulation to allow gradual retraining of the LV. Babies undergoing ASO have a stormy postoperative course because of long bypass time. They require long-term ventilation, sedation and paralysis because of marked LV dysfunction. The critical hemodynamic parameter in postoperative monitoring is the LA pressure, which should remain between 5-8 mm Hg. These patients usually are brought out of operation theatre with LA line in situ. These patients need inotropic support for LV but lower systemic pressures should be tolerated initially and as the LV gets trained, higher pressures are easily tolerated. Fluid boluses should be restricted as far as possible as they are poorly tolerated by the already compromised LV. Milrinone works well in these patients as it gives inotropy as well as afterload reduction. Most neonates undergoing ASO are brought out with peritoneal catheter in situ. This drains the excess fluid that collects in the abdomen. The other reason is that these patients because of poor LV function do not tolerate fluid overload well and threshold to start peritoneal dialysis is low if urine output drops to less than 1 ml/kg/hr. Serum calcium, potassium and glucose hemostasis is critical in such patients and should be managed aggressively. The extensive anatomic dissection, long suture lines and long bypass time predispose to coagulation abnormalities and significant bleeding. This is usually tackled with fresh frozen plasma, platelets and cryoprecipitate. Other important issue in these patients is the coronary reimplantation. Signs of coronary insufficiency should be looked for proactively such as persistent hypotension, rising left atrial pressures, ST-T changes on ECG as it aggravates the LV dysfunction. For this reasons the patients receive nitroglycerine infusion post-operatively. Once bleeding is controlled, these patients are started on heparin infusion and later on aspirin to prevent coronary thrombi along suture lines. Because of marked generalized capillary leak, these babies may have significant myocardial edema, which can create a tamponade like situation once the chest is closed. This may require bringing out the patient open chested and delayed sternal closure.[82]

Total anomalous pulmonary venous connection (TAPVC): In TAPVC, all the pulmonary veins drain outside the left atrium and are connected directly or indirectly to the right atrium. TAPVC may be supracardiac (drain into innominate vein), cardiac (drain into coronary sinus or right atrium), infracardiac (drain into the portal system) or mixed type.[83] The infracardiac variety of TAPVC is usually associated with obstruction and presents medical emergency in the neonatal period. Before discussing the postoperative management, some points need to be highlighted. TAPVC with obstruction is most commonly mistaken in the neonatal period with persistent pulmonary hypertension or hyaline membrane disease so index of suspicion should be high. Secondly, because of obstruction, there is pulmonary venous hypertension, leading to pulmonary arterial hypertension and increased RV afterload. These patients present in the neonatal period with massive pulmonary edema, pulmonary hypertension and congestive heart failure. Thirdly, because of mixing of the oxygenated and deoxygenated blood on the right side of the heart, an atrial level shunt is obligatory to maintain the systemic output. The size of right to left shunt is determined by the size of interatrial communication and the relative resistance of the pulmonary and systemic circulation[84] (Figure 58.7).

Preoperatively these patients are stabilized in the ICU. This includes aggressive management of pulmonary arterial hypertension and congestive heart failure.[85] Postoperative course is related to the preoperative condition and the adaptation of this preoperative condition to the new physiology after repair. Preoperatively the RV is decompressed by right to left shunting at the level of ASD or PDA. On the other hand LV is under loaded because of the absence of direct flow through pulmonary veins. After the surgical correction, both the ventricles face

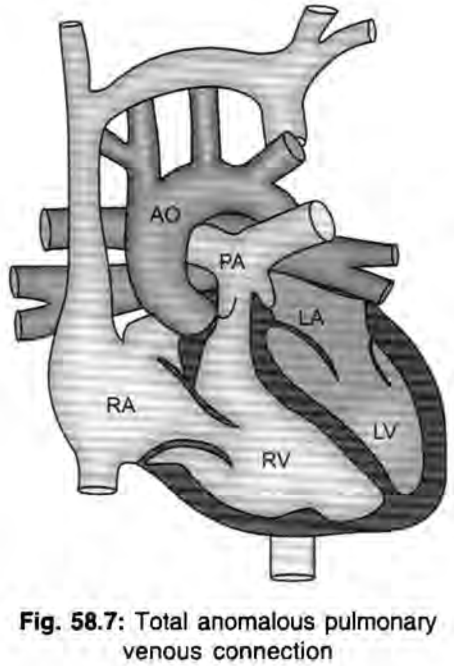


Fig. 58.7: Total anomalous pulmonary venous connection

high afterload and tend to fail. Post-operatively, pulmonary arterial hypertension needs to be managed aggressively – hyperventilation, analgesia, sedation and paralysis, correction of acidosis and pulmonary vasodilatation. Secondly, biventricular dysfunction needs to be assessed and managed with inotropes and afterload reduction. Thirdly, supraventricular arrhythmias occur in about 5-10% of cases of TAPVC which include atrial flutter or fibrillation, reentrant tachycardia and Junctional tachycardia.[86]

Single ventricle complexes: This group of disorders is classified separately because of its uniqueness and complex physiology. The management of these patients is also unique in that these lesions cannot go in for complete anatomical repair and the goal is to achieve physiologic correction.[87] As the name suggests, this group of lesions has only one functioning ventricle that sustains both the pulmonary and systemic circulations. The other ventricle is usually hypoplastic. Tricuspid atresia is the prototype of this group and the basic management of single ventricle complexes has come from the experience of management of this lesion (Figure 58.8). Other lesions managed with this approach are Pulmonary atresia with VSD, Double outlet right ventricle (DORV) with non-committed VSD, Double inlet left ventricle (DILV) with VSD and rarely Double outlet left ventricle (DOLV) with VSD and Double inlet right ventricle (DIRV) with VSD.

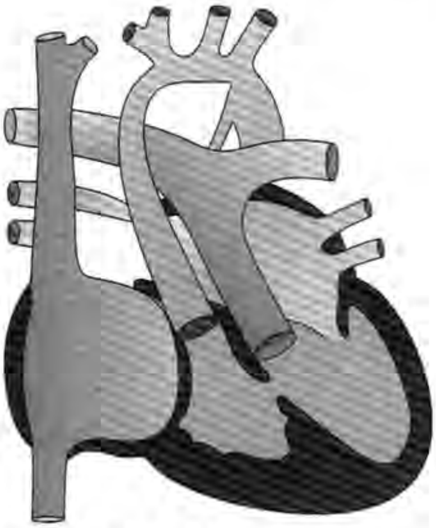


Fig. 58.8: Tricuspid atresia

Studies have shown that the function of the right ventricle or the pulmonary ventricle is only to deliver the blood to the pulmonary circulation and bypassing the right ventricle did not affect the overall cardiac physiology. The left ventricle or the systemic ventricle helps to deliver the cardiac output. Fontan achieved first clinical success in treating patients of Tricuspid atresia. In single ventricle complexes, the functioning ventricle has to sustain for a lifetime and for this it needs to be unloaded and preserved for systemic circulation. This requires separation of the pulmonary and systemic circulations. This is achieved by shunting of the systemic venous return directly into the pulmonary circulation. For this the pulmonary vascular bed should be well developed with low pulmonary vascular resistance. This helps to maintain the pulmonary blood flow, which is driven by the central venous pressure.[88]

The first step in the management of such babies is to protect the pulmonary circulation. Patients with increased pulmonary blood flow need pulmonary artery banding to prevent high flow induced pulmonary hypertension. Patients with decreased pulmonary blood flow require modified BT shunt to improve the cyanosis as well as to facilitate the growth of the pulmonary vascular bed. These procedures are done early in infancy to relieve the symptoms and when the pulmonary vascular resistance has fallen down.[89] These patients require constant follow up till the next staged operations: the Glenn and Fontan. In the Glenn operation, the superior vena cava is separated from the right atrium and attached to the right pulmonary artery. This is usually performed by 1 – 2 years of age by which the pulmonary arteries have grown to a reasonable size. In the Fontan procedure the inferior vena cava is connected to the right pulmonary artery. Fontan outlined the criteria for selection of the ideal candidate for the surgery. The criterion is that the pulmonary circulation is passive and dependent on the transpulmonary pressure gradient between central venous pressure and left atrial pressure. So preoperative assessment is essential to look for any factor that increases the resistance in the whole system, which tends to result in Glenn or Fontan failure. These factors include small pulmonary arteries, elevated pulmonary vascular resistance, conditions that increase the left atrial pressure - mitral stenosis, mitral regurgitation, impaired left ventricular function, aortic valve stenosis and regurgitation, polycythemia – it makes the pulmonary blood flow sluggish. The age of the child is also a risk factor because delaying the procedure increases the risk of paradoxical embolism, chronic hypoxia and sub-aortic obstruction.[90]

Postoperative management of Glenn and Fontan also follows the above criteria. After the Fontan operation the cardiac output is dependent on the pulmonary blood flow and any reduction in the pulmonary blood flow reduces the cardiac output and the oxygen delivery to the tissues. The factors that need to be looked at include hypovolemia, increased pulmonary vascular resistance, distortion of the pulmonary arteries, obstruction of the Glenn or Fontan anastomosis, pulmonary venous obstruction, AV valve regurgitation and systolic or diastolic ventricular dysfunction.[91] Table 58.2 shows the interpretation of the various hemodynamic data and management of low cardiac output.

If there is hypoxemia, one needs to look at the lung causes like atelectasis, pneumonia and pulmonary edema. Most of the patients after Glenn and Fontan procedures are extubated early to prevent lung complications because of prolonged ventilation. If the hypoxemia is disproportionate to the extent of lung disease, right to left intra cardiac shunts should be ruled out by echocardiography. Other cause of hypoxia may be persistent left SVC draining into LA.[92]

All patients undergoing Fontan procedure have systemic venous pressures higher than normal, which leads to transudation of fluid into the interstitium leading to edema, pleural effusions, ascites, hepatic congestion and protein losing enteropathy. Pleural effusions have deleterious effects on PVR and ventricular compliance and cause significant morbidity and require multiple thoracentesis. If the characteristics of the pleural fluid are consistent with chyle, diet modification may also be required.

Rhythm disturbances are common after Fontan procedure most commonly atrial flutter and Junctional ectopic tachycardia. The most common reason atrial dysrhythmia is the exposure of native atrial tissue to high pressure. Junctional ectopic tachycardia may be life threatening and should be managed aggressively. Other significant dysrhythmias after Fontan procedure include complete heart block and sustained supraventricular tachycardia.[93] Atrial flutter and supraventricular tachycardia are

Table 58.2: Algorithm for management of low cardiac output after fontan procedure

Clinical signs:		*Tachycardia, Poor perfusion, Hypotension, Cold extremities, Low urine output*	
S. No.	*Measurement*	*Interpretation*	*Treatment*
1	• CVP < 15 mm Hg • PAP < 15 mm Hg • LAP < 5 mm Hg	• Hypovolemia	• Give fluids until LAP > 8 or CVP – LAP < 7
2	• CVP – PAP > 2 mm Hg	• Obstruction of SVC – PA anastomosis • PA clot	• Thrombolytic therapy • Interventional catheterization • Reoperation
3	• CVP > 18 mm Hg • PAP > 18 mm Hg • LAP < 8 mm Hg	• Pulmonary vasoconstriction • Pulmonary vascular disease • Pulmonary venous obstruction	• Maintain $PaCO_2$ at 30-35 mm Hg • SpO_2 at 100% • pH > 7.5 • PEEP 0 • Normal Glucose, temperature and Calcium
4	• CVP > 18 mm Hg • PAP > 18 mm Hg • LAP > 12 mm Hg	• Ventricular dysfunction • AV valve regurgitation • Ventricular outflow obstruction	• Dopamine and nitroprusside • Milrinone • AV replacement for AV regurgitation • Enlargement of restrictive VSD for sub aortic stenosis

CVP: Central venous pressure, PAP: Pulmonary artery pressure, LAP: Left atrial pressure, SVC: Superior vena cava, PA: Pulmonary artery, AV: Atrio-ventricular, PEEP: Positive end expiratory pressure, VSD: Ventricular septal defect

treated by digitalization and heart block with epicardial demand pacing. Thrombosis in the systemic venous circulation is another important risk factor and the presentation may be that of SVC syndrome (facial plethora) or IVC syndrome (ascites and lower body edema). This may be life threatening and require thrombolytic therapy.

Hypoplastic left heart syndrome (HLHS): HLHS is the term used to describe the spectrum of congenital cardiac malformations that have varying degrees of underdevelopment of left sided heart structures. This group needs special mention because this has been a fatal condition of late and surgical procedure for this lethal disorder has received considerable attention since 1980s.[94] Presently the approach to staged, reconstructive surgery of HLHS is based on the principle that carefully planned and appropriately timed palliative operations should result in suitable physiology for repair by a modification of the Fontan procedure. Norwood described an initial palliative reconstruction allowing survival and growth until PVR decreases.[95] This initial palliation **(Norwood stage I)** results in the construction of neo-aorta and connection of the systemic and pulmonary circulations at the arterial level via a modified Blalock-Taussig shunt. After a period of maturation of pulmonary vasculature, systemic venous return may be directed to the pulmonary arteries (Stages II and III) thus placing the two circulations in series. The goal of Fontan operation is undertaken in stages to reduce the volume load of the ventricle as early as possible.[96] The other option available in this condition is the cardiac transplantation though results of both the options are nearly equal. However in India still the results of the reconstructive surgery are not good and the option of cardiac transplantation is still remote (Figure 58.9).

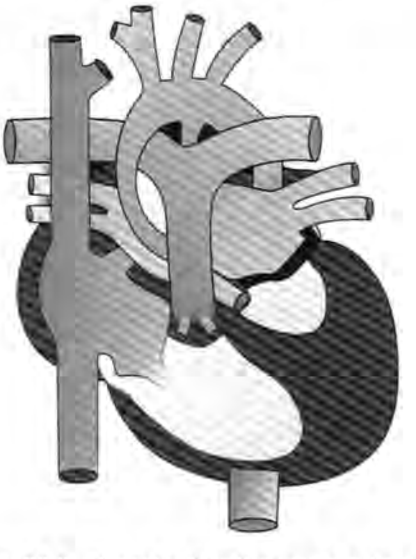


Fig. 58.9: Hypoplastic left heart syndrome

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CHAPTER

Pediatric Pacemaker and Implantable Cardioverter Defibrillator (ICD) Therapy

Frank Zimmerman, Madelyn Kahana, Praveen Khilnani

Cardiac pacing and device therapy for children is being used more frequently and is safer now than in the past in a greater part due to the fact that technology has advanced to make the devices and the implant systems smaller and more efficient as well as improvement in implant techniques. Cardiac pacing in children is primarily used for those with congenital complete heart block. Permanent pacing may be implemented as early as in the newborn period while temporary transvenous or epicardial pacing is frequently utilized in the PICU (pediatric intensive care unit) setting.

Indications

The indications for cardiac pacing in children are expanding as the devices and leads are becoming smaller and safer to implant. Similarly, indications for temporary pacing in the pediatric ICU are expanding to include traditional antibradycardia pacing as well as anti-tachycardia pacing and adjunctive treatment for heart failure. In general, indications for pacing in children are similar to adults, albeit with special considerations that will be discussed in this chapter. The recommendations for permanent cardiac pacing in children specified by the American College of Cardiology (ACC) in 2001 are shown in Table 59.1.[1] A primary indication for pacing is the occurrence of symptoms (such as dizziness, fatigue, syncope) in association with documented bradycardia.[2,3] This includes bradycardia due to sinus node dysfunction or advanced second degree or third degree AV block (complete heart block).

Table 59.1: Indications for pacing in pediatrics

Class 1	1.	Advanced second-or third-degree AV block associated with symptomatic bradycardia, ventricular dysfunction, or low cardiac output.
	2.	Sinus node dysfunction with correlation of symptoms during age-inappropriate bradycardia.
	3.	Post-operative advanced second-or third-degree AV block that is not expected to resolve or persists at least 7 days after cardiac surgery.
	4.	Congenital third-degree AV block with a wide QRS escape rhythm, complex ventricular ectopy, or ventricular dysfunction.
	5.	Congenital third-degree AV block in the infant with a ventricular rate less than 50 to 55 bpm or with congenital heart disease and a ventricular rate less than 70 bpm.
	6.	Sustained pause-dependent VT, with or without prolonged QT, in which the efficacy of pacing is thoroughly documented.
Class 2a	1.	Bradycardia-tachycardia syndrome with the need for long-term antiarrhythmic treatment other than digitalis.
	2.	Congenital third-degree AV block beyond the first year of life with an average heart rate less than 50 bpm, abrupt pauses in ventricular rate that are two or three times the basic cycle length, or associated with symptoms due to chronotropic incompetence.
	3.	Long-QT syndrome with 2:1 AV or third-degree AV block.
	4.	Asymptomatic sinus bradycardia in the child with complex congenital heart disease with resting heart rate less than 40 bpm or pauses in ventricular rate more than 3 seconds.
	5.	Patients with congenital heart disease and impaired hemodynamics due to sinus bradycardia or loss of AV synchrony.

Contd...

Contd...

Class 2b	1. Transient post-operative third-degree AV block that reverts to sinus rhythm with residual bifascicular block.
	2. Congenital third-degree AV block in the asymptomatic infant, child, adolescent, or young adult with an acceptable rate, narrow QRS complex, and normal ventricular function.
	3. Asymptomatic sinus bradycardia in the adolescent with congenital heart disease with resting heart rate less than 40 bpm or pauses in ventricular rate more than 3 seconds.
	4. Neuromuscular diseases with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease.
Class 3	1. Transient post-operative AV block with return of normal AV conduction.
	2. Asymptomatic post-operative bifascicular block with or without first-degree AV block.
	3. Asymptomatic type I second-degree AV block.
	4. Asymptomatic sinus bradycardia in the adolescent when the longest. RR interval is <3 seconds and the minimum heart rate is >40.

The most common cause of complete heart block in children with structurally normal hearts is maternal lupus.[4] The risk for sudden cardiac death in these patients if untreated is approximately 5 to 8 percent.[5] Risk factors for sudden death in asymptomatic children with complete heart block prompting early intervention with pacing include low resting heart rates (based on age), a wide complex QRS escape rhythm or prolonged QT interval.[6-9] Some long-term studies have shown that the incidence of sudden death in patients with no previously known risk factors is significant and lifelong and suggest elective pacemaker implantation prior to the second or third decade of life in this group.[5] Children with congenital heart disease and complete heart block have a high incidence of sudden cardiac death of approximately 28 percent and thus early intervention with pacing is usually recommended.[10] Complete heart block in the post-operative period, which is not resolved within seven days, is also an indication for permanent pacemaker implantation as there is an 80 to 100 percent incidence of sudden death over a two-year period.[11,12]

Other indications for cardiac pacing in children include cardiomyopathy associated with conduction abnormalities such as Kearne-Sayre syndrome, treatment for syncope not responsive to medical therapy, prolonged QT syndrome and treatment for obstructive hypertrophic cardiomyopathy in an attempt to decrease the left ventricular outflow tract gradient.[13-16]

Temporary pacing is often utilized in acute situations to stabilize patients who are ultimate candidates for permanent pacemaker implantation. Other indications for temporary pacing include transient sinus node dysfunction or heart block due to medications, metabolic causes, following myocardial infarction or in the post-operative period while waiting for recovery. Infectious etiologies, such as endocarditis or Lyme's disease, are associated with a 10 percent incidence of transient complete heart block.[17] Also, acute ventricular arrhythmias such as torsades de pointes seen in association with prolonged QT syndrome can often be prevented with overdrive ventricular pacing.[18] Other therapeutic indications for temporary pacing including anti-tachycardia pacing for reentrant arrhythmias will be discussed later in the chapter.

Pacemaker Basics (Fig. 59.1)

Threshold and Output

Cardiac pacing involves the delivery of an electrical impulse to the myocardium of sufficient strength and duration to elicit a propagation of cardiac action potentials. The minimum amount of electrical energy required to stimulate the muscle is known as the pacing threshold. The threshold energy is related to the intensity or strength of the impulse as well as the duration of time for which it is delivered. Appreciation of this exponential relationship (strength-duration curve) is important for proper programming of pacemaker outputs to ensure capture of paced beats.[19-21]

Fig. 59.1: Pacemaker *(For color version see Plate 11)*

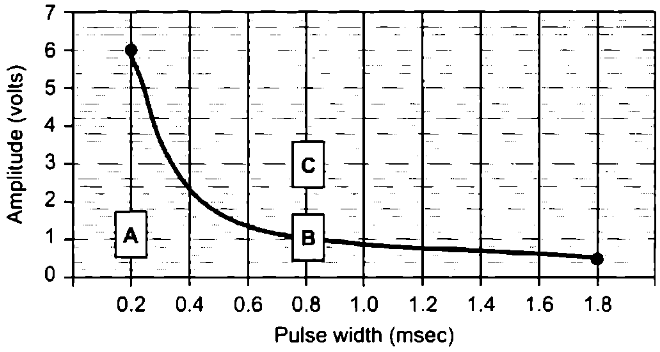


Fig. 59.2: Strength duration curve is depicted. This is generated by determining the pacing threshold amplitude (volts) at each pulse width (milliseconds, msec). The black curved line is the threshold curve. Pacing outputs at point A (1 volt and 0.2 msec) would be below threshold and not capture or pace the heart. Outputs at point B (1 volt and 0.8 msec) would be at threshold and would pace the heart but there is no "safety" margin if the threshold curve would change. Outputs at point C (3 volts and 0.8 msec) would not only pace the heart but there would be a three times "safety" margin based on the threshold curve

Permanent pacemakers are powered by lithium iodine batteries that deliver constant voltage outputs. This means that the operator can program a desired voltage output as well as the duration of time (pulse width) the output is to be delivered. In order to select optimal pacemaker outputs, a strength-duration curve is first generated (Fig. 59.2). This is performed by manually or automatically decreasing the output voltage while maintaining fixed pulse width until there is loss of capture. The threshold voltage is the minimum voltage output that captures the myocardium. For instance, if pacing at 2.5 volts and 0.5 msec captures the heart but there is no capture at 2.0 volts and 0.5 msec, then the threshold is 2.5 volts at 0.5 msec. Once pacing thresholds are determined, the pacemaker is programmed to a voltage output of approximately twice that of the threshold value in order to maintain an adequate "safety margin" for pacing. In the above example, the pacemaker would be programmed at 5 volts and 0.5 msec to ensure an adequate safety margin for pacing. This is required because myocardial thresholds vary with time and can be affected by medications, metabolic status, exercise or scar tissue formed around the leads.[22-24]

Temporary pacemaker devices are usually powered by disposable batteries and deliver a constant current output. The pulse width is usually fixed at a preset value and cannot be reprogrammed. Therefore, the operator can program only the output current (measured in milliamps) much the same way as described for permanent pacemakers. Again, at least a two to three times safety margin for pacing is preferred, however, because preservation of battery life is not an issue with temporary pacemakers, outputs of five to ten times the threshold are not uncommonly programmed. The use of higher safety margins with temporary pacing systems may also be desirable because temporary pacing wires have unstable threshold values that may increase rapidly or unpredictably compared to permanent pacemaker leads.[25]

Sensing

Sensing of intrinsic or paced beats is important for any pacemaker system in order to avoid inappropriate pacing[26] or inadvertent inhibition of pacing. The sensing of a pacemaker system is usually measured in millivolts and can be likened to setting the height of a wall (Figs 59.3A to C). The pacemaker will sense signals that are higher than the wall. If the height of the wall is low (lower mV setting) then sensing will be increased. Oversensing occurs when the pacemaker detects noise or artifact on the lead and labels this as intrinsic cardiac activity. This may lead to inappropriate inhibition of pacing and can be corrected by decreasing pacemaker sensitivity

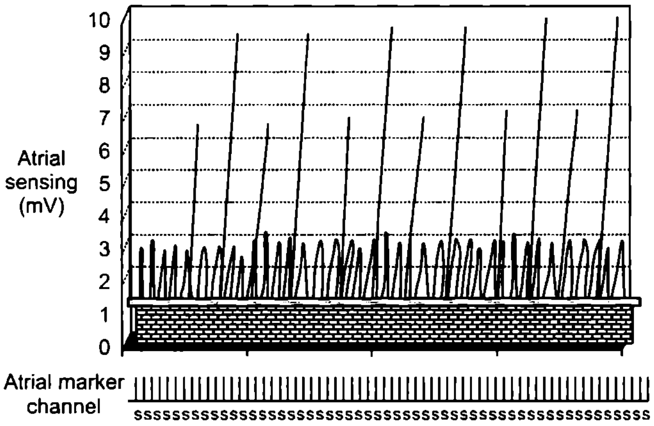


Fig. 59.3A: Atrial sensing in millivolts (mV) is depicted in the graph. The electrograms (black lines) represent atrial signals and include noise (low amplitude frequent signals) as well as larger atrial signals with varying amplitude. The sensing (brick wall) is set at 1 mV. Thus, any signal greater than 1 mV amplitude is sensed by the pacemaker. The atrial marker channel shows the atrial signals that are sensed(s)

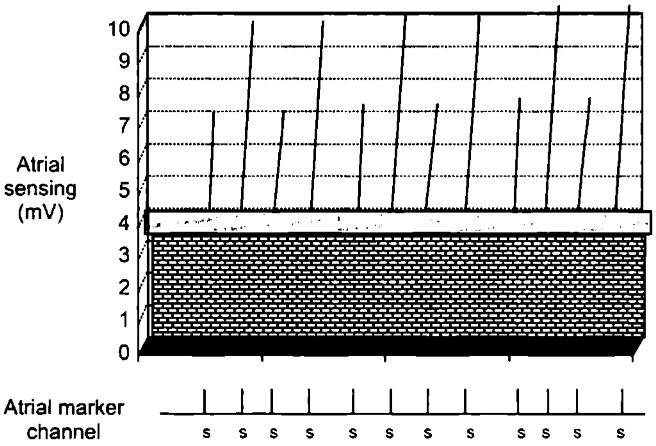


Fig. 59.3B: Atrial sensing in millivolts (mV) is depicted in the graph. The electrograms (black lines) represent atrial signals and include only larger atrial signals with varying amplitude. The sensing (brick wall) is set at 4 m V. Thus, any signal greater than 4 m V amplitude is sensed by the pacemaker. The atrial marker channel shows the atrial signals that are sensed(s)

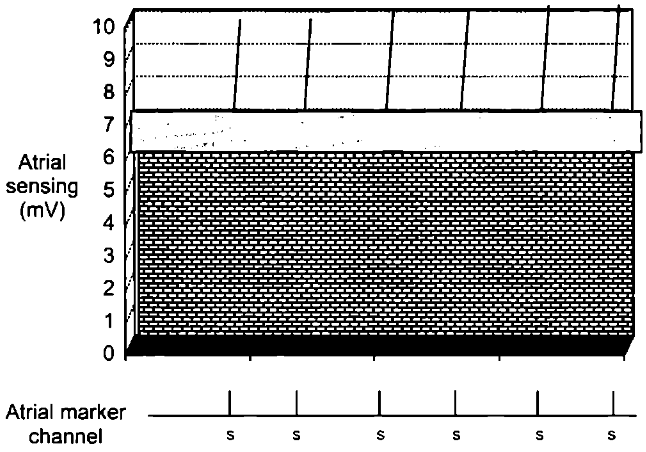


Fig. 59.3C: Atrial sensing in millivolts (mV) is depicted in the graph. The electrograms (black lines) represent atrial signals and include only larger atrial signals. The sensing (brick wall) is set at 7 mV. Thus, any signal greater than 7 mV amplitude is sensed by the pacemaker. The atrial marker channel shows the atrial signals that are sensed(s)

(increasing the wall height). Undersensing occurs when intrinsic cardiac activity is not sensed by the pacemaker and is corrected by increasing sensitivity (decreasing the wall height).

Pacemaker Hardware

Generator

Permanent pacemaker generators usually consist of a metallic can containing the circuitry and lithium iodine battery. They also consist of a plastic header which connects to the pacemaker leads. The pacemaker generator can be usually placed in a subcutaneous pocket either in the chest or the abdomen. A submuscular pocket may be more appropriate for thin or young patients as this affords more protection to the pacemaker system.[27,28] Temporary pacemakers have various programmable features and settings that are usually run on 9-volt disposable batteries.

Pacemaker Leads

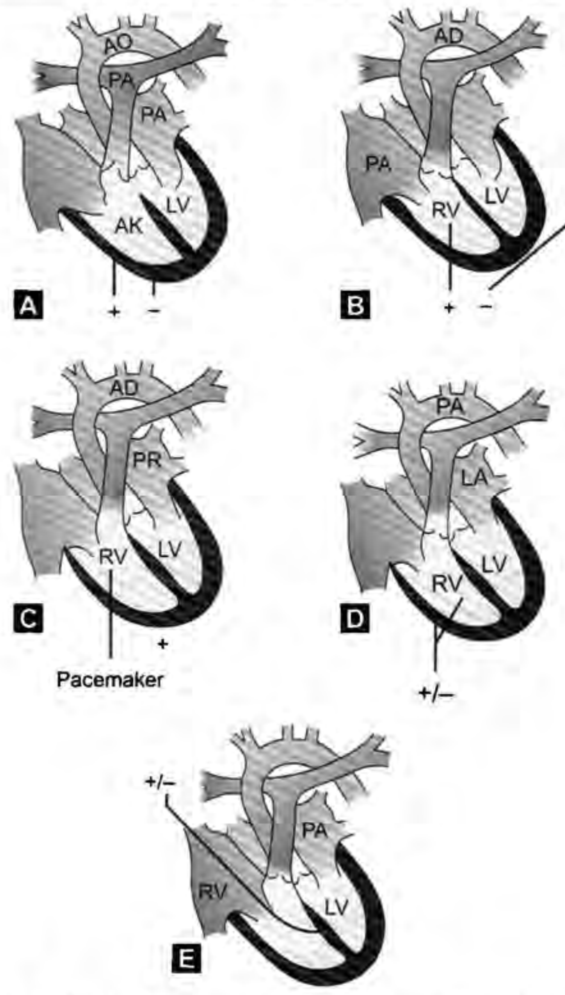
The pacemaker lead is utilized to transfer the energy from the pacemaker generator to the myocardium. The tip of lead where electrons exit into the myocardium is traditionally labeled as the negative pole or cathode. To complete the circuit, the electrons must pass through the myocardium and back to a positive pole or anode. In a bipolar system the negative pole and the positive pole are both in contact with the myocardium. In transvenous leads, the negative pole is at the tip and the positive pole is a ring on the same lead very near the tip. In epicardial systems, two separate unipolar leads or a single lead with a "y" adaptor are placed on the myocardium (Fig. 59.4). In a unipolar system, the negative pole is in contact with the myocardium and the positive pole may be either a lead on the patient's skin or the permanent pacemaker generator itself.

Transvenous endocardial leads are most commonly utilized in permanent pacemaker systems and are characterized by either active fixation where a screw is extruded from the tip and to the muscle or passive fixation where fins or tines at the lead tip become entangled in the atrial or ventricular trabeculae. Epicardial leads are either shown to the surface of the heart or can also be screwed into the myocardium. The leads are coated in silicone or polyurethane for insulation and recently leads have a small amount of steroid at the tip in order to prevent scar formation and thus decrease the overall pacing thresholds.[29,30] Temporary pacing leads are sutured to the surface of the heart while a second lead (anode) may be placed directly into the skin.

Pacemaker Programming

Pacemaker Code

The pacemaker code can be seen in Table 59.2.[31] The first letter represents the cardiac chamber that is



Figs 59.4A to E: Various pacing configurations. Panel A shows epicardial bipolar pacing utilizing two temporary unipolar wires. Panel B shows unipolar epicardial pacing utilizing a temporary wire connected to the skin as the positive pole (anode). Panel C shows unipolar epicardial pacing in a permanent system with the pacemaker generator serving as the anode. Panel D shows bipolar epicardial pacing utilizing a single lead with a "y" adaptor. Panel E shows bipolar pacing utilizing a bipolar transvenous lead (tip is negative pole and a ring near the tip is the positive pole)

paced. This can be the atrium, ventricle, both or neither. The second letter represents the cardiac chamber that is sensed and again can represent the atrium, ventricle, both or neither. The third letter is the response of the pacemaker and can include inhibition, triggering, both or neither. Inhibition occurs when the pacemaker senses intrinsic cardiac activity and withholds pacing. Triggering occurs when the pacemaker senses an intrinsic beat and then paces at a set interval following that beat. For example, with dual chamber pacing, an atrial sensed beat triggers the ventricle to be paced (tracking of the atrial beats). The fourth letter is for permanent pacemakers that have additional features (e.g. rate response or antitachycardia pacing features).

Pacemaker Timing Intervals

For single chamber pacing the most important timing feature is the rate limit. This sets the pacing rate of the pacemaker if it does not sense intrinsic activity. If the intrinsic rate is above the rate limit, pacing will be inhibited. For dual chamber pacing, this becomes the lower rate limit. An upper rate limit is also programmed but is limited to 180-200 bpm depending on the pacing system. The upper rate sets the limit that the pacemaker will track intrinsic activity. For example, a dual chamber system is programmed at a lower rate of 60 bpm and upper rate of 120 bpm for a patient with complete heart block and an atrial rate of 80 but a ventricular rate of 40. The pacemaker would respond by tracking the atrium and pacing the ventricle at a rate of 80 bpm. If the atrial rate decreased less than 60 bpm, the pacemaker would respond by atrial and ventricular pacing at the lower rate limit of 60 bpm. If the atrial rate exceeded 120 bpm, the pacemaker would try to track the atrial rate but there would eventually be dropped beats. This irregular rhythm with dropped beats is known as pacemaker Wenckebach block. An AV interval may also be programmed in dual chamber systems and is analogous to the PR interval on the EKG. Another common timing interval is called the PVARP, or postventricular atrial refractory period. This is a programmable time occurring after a paced or sensed ventricular event during which the atrial lead will not sense any signals. This is used to avoid inappropriate sensing of retrograde p-waves. The PVARP is often shortened in order to allow for increased levels of upper rate tracking.

Common Pacemaker Modes

AAI: Atrial pacing with *Atrial* sensing, with *response to atrial sensing being Inhibitory*, i.e. intrinsic sinus node impulse is allowed to propagate and the pacemaker is inhibited for that beat to avoid erratic electrical activity. AAI pacing is performed in patients with

Table 59.2: NASPE/BPG pacemaker code

I *Chamber paced*	*II* *Chamber sensed*	*III* *Response to sense*	*IV* *Program/Rate modulation*	*V* *Anti-tachycardia function*
O	O	O	O	O
A	A	T	P(1)	P(2)
V	V	I	M	S
D (A+V)	D (A+V)	D (T+I)	C	D (P+S)
			R	

A=atrium; C=communicating; D=dual; I=inhibited; M=multiprogrammable; O=none; P(1)=simple programmable; P(2)=antitachyarrhythmia pacing; R=rate modulation; S=shock; T=triggered; V=ventricle

intact intrinsic AV node conduction but with bradycardia due to sinus node dysfunction, medications, drugs, CNS disease, or other etiologies. A rate responsive mode (AAIR) can also be programmed in permanent pacemakers in order to achieve increased heart rates when the pacemaker senses increased activity or motion. In the AOO mode, atrial pacing is performed asynchronously at the rate that is set regardless of any intrinsic atrial activity. This mode may be programmed if there is no evidence for intrinsic atrial activity and in order to avoid any atrial oversensing which would inappropriately inhibit the pacemaker.

VVI: Ventricular paced, *Ventricular* sensed and *response to ventricular sensing being Inhibitory*. VVI pacing is performed for similar reasons as AAI pacing but for those patients in whom either atrial pacing cannot be achieved or in which there is no intrinsic AV conduction. Similarly to the AAI mode, VVI pacing would be inhibited if the intrinsic ventricular rhythm were greater than the rate limit. In the VOO mode, there is asynchronous ventricular pacing.

DDD means dual chamber pacing, dual chamber sensing and dual response of triggering and inhibition (D stands for dual chamber, atrium and ventricle). DDD pacing is the most physiologic type of pacing in patients with complete heart block. Intrinsic atrial activity is tracked when between the lower and upper rate limits and ventricular pacing is performed once the programmed AV delay has occurred. Atrial and ventricular pacing can be inhibited if the patient's intrinsic rhythm occurs.

VDI pacing is programmed if atrial pacing is not achievable but atrial sensing is intact.

Pacemaker Hemodynamics

The ultimate goal for cardiac pacing would be to achieve the most physiologic hemodynamic response as possible. This is usually primarily achieved by maintaining AV synchrony, which accounts for approximately 25 percent of cardiac output at rest (Fig. 59.5).[32] Pacing rate and optimal AV interval is also important to optimize cardiac output in compromised conditions or during exercise.[33-36] Finally biventricular pacing is now recognized as therapy for patients with low cardiac output and either bundle branch block or intraventricular conduction delay.[37,38] In this type of pacing, both the right and left ventricles are stimulated simultaneously in order to improve co-ordination and contraction of the ventricles and improve cardiac output.

Atrial Electrogram

Recordings from the atrial pacemaker leads (atrial electrogram) are often useful to distinguish atrial

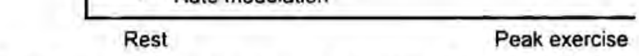
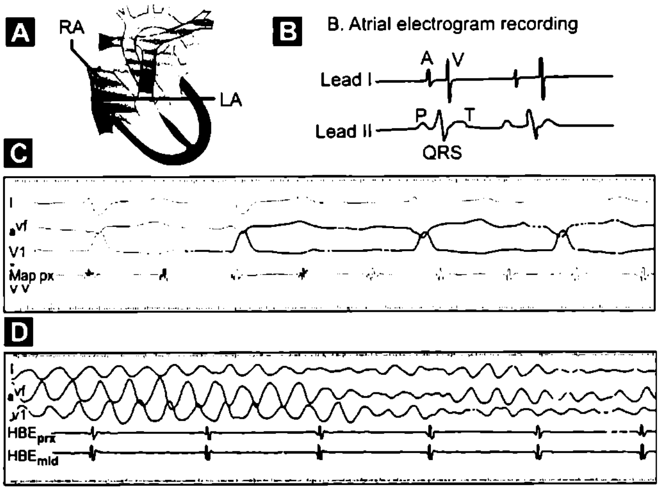


Fig. 59.5: Pacemaker hemodynamics. Theoretical graph showing that the benefit of AV synchrony is greatest at rest while rate response (modulation) is most beneficial for cardiac output during exercise



Figs 59.6A to D: Atrial electrogram recordings are obtained by connecting the right atrial epicardial leads to the ECG right arm (RA) and left arm (LA) electrodes (shown in panel A). Panel B demonstrates the electrogram recording in lead I compared to the surface lead II. Because the atrial activity is more clearly seen with the electrogram recording, it is easier to diagnose atrial tachycardias such as atrial flutter (panel C) and ventricular tachycardia with atrial dissociation (panel D)

activity and help diagnose arrhythmias when the p-waves on the surface ECG are difficult to identify (Fig. 59.6).

Common Pacing Scenarios in the PICU

Bradycardia is a common scenario where either temporary or permanent pacing may be required. Bradycardia can be seen in the post-operative period following cardiopulmonary bypass or secondary to metabolic causes, medication side effects or infectious processes. If AV conduction is intact, atrial pacing alone can provide sufficient support. However, in most cases with bradycardia, AV conduction is also effected and thus pacing in the DDD mode or VVI mode is required.

Post-operative junctional ectopic tachycardia (JET) can be seen following certain types of congenital heart disease surgery or can be associated with low cardiac output and metabolic abnormalities, such as acidosis or electrolyte problems. Hemodynamic compromise is due to the rate of tachycardia as well as loss of AV synchrony. While the tachycardia is usually treated with cooling, correction of metabolic abnormalities or use of antiarrhythmic medications, atrial pacing at a rate faster than the tachycardia can be used to re-establish AV synchrony.

Pause dependent ventricular tachycardia (VT) can be seen with acquired or congenital prolonged QT syndrome. The characteristic polymorphic VT (torsade de pointes) is a key feature for this diagnosis. Atrial or ventricular pacing used to prevent bradycardia or sinus pauses that precede the development of ventricular tachycardia can be useful for decreasing the frequency of ventricular dysrhythmias.

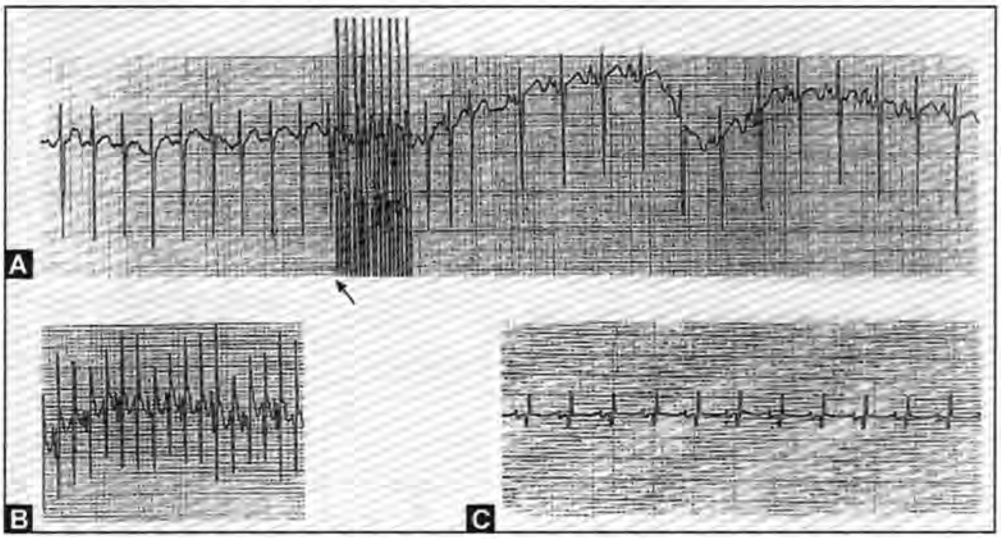
Reentrant forms of tachycardia can often be terminated with atrial or ventricular pacing. Reentrant atrial tachycardia, such as atrial flutter or sinus node reentry, can be terminated with atrial pacing whereas other tachycardia, such as AV node reentry or atrioventricular reentry tachycardia using an accessory bypass tract, may respond to either atrial or ventricular pacing. Some forms of ventricular tachycardias have a reentrant mechanism that may also respond to ventricular pacing and occasionally to atrial pacing.

Antitachycardia Pacing

The goal of antitachycardia pacing is to interrupt a reentrant tachycardia circuit with premature paced beats.[39,40] There are several methods that can be used to achieve this goal. The most common is to perform rapid atrial or ventricular pacing at a fixed rate greater than the rate of tachycardia. One typically starts at a rate 5-10 bpm faster than the tachycardia (Fig. 59.7). Pacing should be performed at maximum outputs as pacing thresholds may be slightly increased during tachycardia. The maximum heart rate during pacing that is considered safe varies with age. Another method is to ramp or slowly increase the rate during antitachycardia pacing.

Finally, application of premature extra stimuli may be used to terminate tachycardia. For example, a regimen consisting of a train of eight paced beats followed by several premature beats is often employed. In order to perform this type of antitachycardia pacing, one must have a specialized pacemaker system with the ability for this programming.

The risk of rapid antitachycardia pacing is that a stable reentrant tachycardia may inadvertently be converted into a more unstable type of tachycardia, such as atrial fibrillation with rapid ventricular response or ventricular fibrillation. It is for this reason that resuscitation equipment, including an external defibrillator, should be readily available while performing these maneuvers.



Figs 59.7A to C: Atrial antitachycardia pacing. Panel A shows a surface ECG lead of atrial flutter that is converted to sinus rhythm with burst atrial pacing (arrow) using an esophageal pacing electrode. Panel B shows the atrial electrogram of atrial flutter before pacing. Panel C shows the atrial electrogram following pacing

Implantable Cardioverter Defibrillator (ICD)

The ICD is widely used in the adult population, mainly for primary and secondary prevention of sudden death in patients with decreased cardiac function following myocardial infarction. It is gaining increasing use in pediatrics as devices and leads are smaller and safer to implant.[41]

ICD Basics

ICD hardware systems are similar to pacemaker systems and all ICD's can function as pacemakers.[42] In addition, ICD's are capable of delivering a shock internally to the heart if a tachyarrhythmia is detected. Most detection algorithms are based on a set rate, above which is labeled as tachycardia. In order to achieve this, the ICD can is larger than a pacemaker to accommodate larger capacitors. Furthermore, the transvenous ventricular lead is larger to accommodate a shock coil.[43] Epicardial patches placed around the heart in the pericardium can also be used. An example of ICD detection and shock is shown in Figure 59.8.

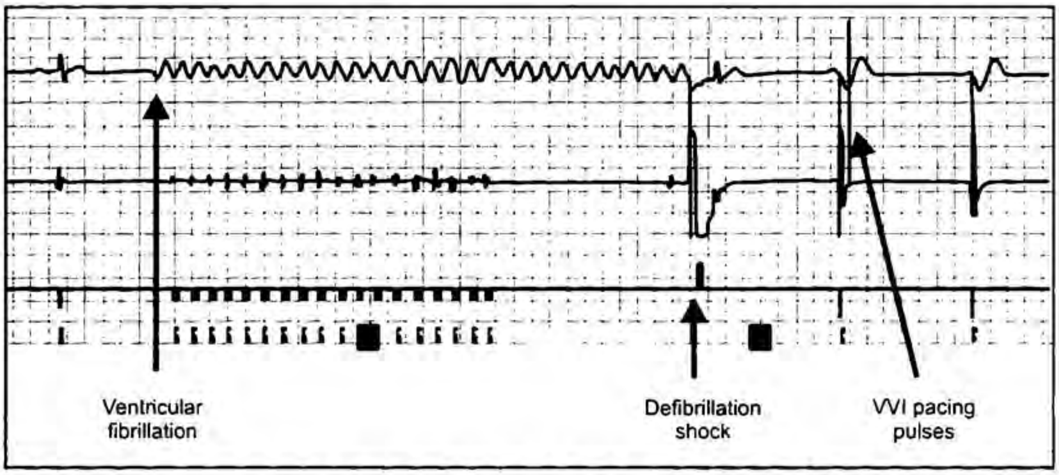


Fig. 59.8: Electrograms from an implantable cardioverter defibrillator. The first line is a modified surface ECG lead and shows the acute onset of ventricular fibrillation. The second line is the ventricular electrogram and the third line is the marker channel. The ICD detects the rhythm and delivers a defibrillation shock, converting the rhythm to a ventricular paced rhythm (VVI pacing)

Risks

The risks associated with pacemaker or ICD implant include infection, bleeding, cardiac perforation, and inadvertent heart block during lead manipulation.[44,45] A major concern in younger patients is the risk for venous stenosis or occlusion associated with transvenous leads. As many of the pediatric patients will require lifelong pacing, consideration of preserving venous access should be accounted for when deciding between an epicardial or transvenous approach to pacing. An issue that arises with ICD implantation is the occurrence of inadvertent shocks. This is a particular problem with children as sinus rates during exercise and may exceed the detection rate for tachycardia and lead to an inadvertent shock. The risks of temporary pacing include cardiac perforation or infection. There is a 25 percent incidence of lead dislodgement reported leading to loss of capture.[46]

Future Considerations

Pacing in children has undergone dramatic changes mainly due to advances in technology that have led to smaller leads and pacemaker generators. As this continues, pacing in children will be safer and may help to overcome issues such as venous stenosis or occlusion. Also, as more patients survive surgery for congenital heart disease, late problems such as sinus node dysfunction requiring intervention with pacing or ventricular arrhythmias requiring ICD implant will become more prevalent. Finally, the possibility of biventricular pacing as adjunctive therapy for heart failure may be applied to select children as it now is gaining widespread use in adults.

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CHAPTER

Interventional Pediatric Cardiology: An Overview

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Over the past decade, the scope of pediatric catheterization laboratory has changed dramatically from a primary diagnostic facility to a conduit for therapeutics. While the first application of catheter interventions was described over 38 years ago by Rubio-Alvarez, it was not until 1966, when Rashkind and Miller described the technique for percutaneous creation of an atrial septal defect in the setting of complete transposition of the great arteries, did such catheter maneuvers decisively impact patient management.[1-8]

Such interventions may be corrective, reparative, or palliative (Table 60.1). Lesions that may be amenable to repair include typical pulmonary valve stenoses, recoarctation of the aorta, and the persistently patent arterial duct. Newer approaches may extend this list to selected patients with atrial and muscular ventricular septal defects. Palliation may be accomplished in lieu of surgery, or as an adjunct in a staged approach to patient care. Lesions amenable to such palliation include aortic stenosis, residual post-operative systemic or venous obstructions, native coarctation of the aorta, stenotic prosthetic tissue valves, and congenital pulmonary arteriovenous fistulae. Catheter therapies may also be applied as adjuncts to surgery, include embolization of systemic-to-pulmonary artery collaterals, surgically created systemic-to-pulmonary shunts, venous obstructions, interatrial communications, and peripheral pulmonary arterial stenosis. Therapeutic interventions, as with cardiac surgery, have three principal objectives: improvement and/or preservation of cardiac function, improvement in longevity, and maintenance or improvement in the quality of life. When these objectives are met, interventional catheterization obviates the surgical morbidity and mortality. Unsuccessful outcomes, including complications and nondefinitive outcomes, may in part yield to experience and improvements in technique.[9]

Table 60.1: Various cardiac lesions subject to intervention

Lesions Amenable to Repair
- Pulmonary stenosis
- Recurrent coarctation of the aorta
- Persistent arterial duct
- Atrial septal defect
- Muscular ventricular septal defects

Lesions Amenable to Palliate
- Aortic valve stenosis
- Postoperative systemic or venous obstructions
- Native coarctation of the aorta
- Obstructed prosthetic tissue valves
- Pulmonary arteriovenous malformations

Lesions Amenable to Palliation or Surgical Correction
- Systemic to pulmonary collaterals/shunts
- Venous obstructions (systemic/pulmonary)
- Intra-atrial communications
- Peripheral pulmonary artery stenosis

VASCULAR ANGIOPLASTIES

Mechanism of Dilation

Histologically, vascular stenoses present a spectrum from normal to exaggerated medial or intimal hyperplasia with alterations in the proportions of elastin, collagen, and smooth muscle, with those lesions acquired after surgery having additional mural and perivascular fibroses. Successful angioplasty results in longitudinal or oblique, intimal or medial tears with organization of intramural hemorrhage and scar formation as a mode of healing. Neoendothelialization is complete in 3 to 6 weeks, while areas of mural thinning within the scar may predispose to aneurysm formation. Post-operatively, the perivascular fibroses may reinforce the outer vessel wall and lessen balloon angioplasty risk. Several months must be allowed after surgery to afford complete tissue granulation and to avoid transmedial tears during the procedure.

Dilation of Pulmonary Artery Stenosis

Stenosis of the proximal pulmonary arteries or their branches may occur as a primary congenital lesion (*de novo* or as a component of Fallot's tetralogy) or a residua of surgical repairs or shunts. As such, they may lead to significant maldistribution of pulmonary blood flow, right heart failure and right ventricular hypertension, and be a significant cause of mortality after biventricular or univentricular (Fontan) repair.

Surgical approaches are of limited success in addressing this lesion and approaches are frequently confined to the proximal branches.

Balloon dilation is clinically well tolerated and should be considered as the initial form of intervention, carrying a low morbidity risk and 1 to 2 percent mortality. Although angiographic improvement in vessel caliber (> 50% increase in vessel diameter) can be achieved in half the patients, restenosis is common (15 to 20%) and long term clinical benefit is achieved in < 35 percent of patients.[10] The procedure has been applied in the supravalvular pulmonary stenosis soon after the arterial switch procedure, with little clinical improvement.

Dilation of Coarctation of the Aorta

Coarctation of the aorta may lead to profound heart failure in the newborn. In the older patient, systemic hypertension, vascular, and myocardial sequelae predispose to endarteritis, aneurysms, and dissection. Surgery is recommended before the age of 2 to 4 years to lessen the incidence of persistent hypertension. The incidence of reoperation in patients repaired in early infancy (particularly the newborn period) is significantly higher (10 to 30%) than those repaired beyond one year of age. Surgery for recurrent coarctation is difficult and has an associated increased morbidity. Percutaneous balloon angioplasty is the treatment of choice in restenosis after surgical repair, irrespective of surgical technique.

Balloon angioplasty for previously unoperated (native) coarctation is controversial. Application in the newborn period has been studied and shown to be ineffective with recurrent stenosis occurring as early as 2 weeks after the procedure. The incidence of aneurysm formation (6 to 45% in various series) and insufficient gradient reduction has prompted some to reserve such procedures to recurrent lesions only. However, aneurysms can be found after surgical prosthetic patch angioplasty (5 to 21% after 10 years) and after subclavian flap aortoplasties. Cystic medial necrosis within the coarcted segment and the development of aneurysms suggest an intrinsic substrate for their formation. At present, the long-term risk of aneurysm formation, changes in wall structure, and the risks of restenosis cannot be determined. Remodeling of the aorta has been described after successful balloon angioplasty, suggesting normalization of flow results in optimal growth of the aortic segments. Patients may be discharged within 24 hours of the procedure, but careful follow-up is encouraged with chest radiographs, echo-cardiograms, and magnetic resonance imaging to detect aneurysm formation.

Dilation of Systemic and Pulmonary Obstructions

Systemic and pulmonary venous obstructions can occur after atrial switch procedures. Baffle stenosis can result in venous congestion, pulmonary edema, reduced exercise tolerance, and heart failure. Balloon angioplasty appears to be the initial treatment modality based upon several centers experiences. The criteria for balloon intervention are the same as those for surgery.

Pulmonary vein stenosis, on the other hand, whether congenital or surgically acquired, has had disappointing results, either being nondilatable or developing early restenosis. These stenoses can appear discrete with intimal hyperplasia and fibrosis, but frequently, and not apparent on angiography, they have involvement of long vessel segments that complicate local attempts at repair. Surgical approaches have similarly high restenosis rates. The application of endovascular stents appears promising although long segment lesions and the timing of intervention in terms of their progressive nature are important affecting a good outcome.

Dilation of Miscellaneous Vascular Lesions

Balloon dilation has been applied in the setting of fibromuscular dysplasia and Takayasus' arteritis with partial success. Aortopulmonary collaterals, in the setting of pulmonary atresia and ventricular septal defect, have been unsuccessfully dilated. A number of reports have noted improvement in oxygen saturation in dilation of stenotic surgically created aortopulmonary shunts. The potential application of endovascular stents may be useful in these situations.

DILATION OF VALVULAR LESIONS

Morphology

Typical valvular stenoses are characterized by fused, partially absent, or underdeveloped commissures with a small eccentric orifice. Echocardiographic, intraoperative, and postmortem examinations have documented commissural splitting as the mechanism of dilation, often with complete separation of the previously fused leaflets. Extracommissural tears and avulsions of the valve leaflets may occur as the disruptions develop along areas of least resistance and result in various degrees of valve, insufficiency, more likely in unicommissural valves. Pulmonary valve dilation has been shown to be safely accomplished with balloons 20 to 40 percent larger than the valve annulus, while aortic valve dilations are tolerated best with balloons no larger than 10 percent of the annulus diameter. Residual gradients and the degree of insufficiency remains unchanged in medium-term follow-up.

Dilation of the Pulmonary Valve

Severe pulmonary valve stenosis may lead to right heart failure and cyanosis if an atrial defect is present. A dynamic infundibular muscular obstruction is common, particularly in long-standing and severe lesions. Surgical mortality for pulmonary valvotomy is < 10 percent for patients < 2 years of age and < 0.5 percent in older individuals. Gradients < 25 mmHg were found in 81 percent of surgically treated patients < 5 years after valvotomy. Pulmonary insufficiency was present in 50 percent, and infrequently, the cause of any clinical symptoms.

Several hundred balloon dilations of the pulmonary valve have been reported and the procedure has surpassed surgical valvotomy as the treatment of choice. Arbitrarily, the indications for balloon dilation in our unit have been set at a transvalvular echographically detennined gradient of 40 mmHg. Patients with dysplasia of the pulmonary valve leaflets have also undergone dilation with varying degrees of success, those with hypoplastic pulmonary valve rings having the least effective procedures. Balloon angioplasty of the pulmonary valve has similarly been applied in children with complex forms of cyanotic heart disease, such as Fallot's tetralogy with some success in improving systemic oxygenation.

Systematic evaluation of the pulmonary valve annulus, pulmonary arterial growth, or the subsequent need of transannular patch enlargement at surgical correction needs further study. Dilation in the neonate with isolated disease has been encouraging with a number of series documenting transvalvular gradient reduction < 35 mmHg. Balloon dilation appears to provide long-term gradient relief in the majority of patients, with regression of subpulmonary muscular obstruction.When using balloons 20 to 40 percent larger than the pulmonary valve annulus, the average gradient is reduced by 75 percent to < 25 mmHg in 93 percent of patients. Using balloons < 20 percent of the valve annulus, the average gradient reduction is 50 to 70 percent with residual gradients below 25 mmHg in 75 percent of patients. In 353 patients abstracted by McCrindle and Kan[11] from 15 studies, acute success ranged from 37 to 100 percent (successful procedures defined as gradients < 36 mmHg), with 283 patients (80%) having successful procedure.

Dilation of the Aortic Valve

Aortic stenosis can precipitate ventricular failure and subendocardial ischemia. Severe stenosis is associated with a 19 percent risk of sudden death, and the lesion is often progressive. Surgical therapy beyond infancy carries a 2 percent mortality. In large referral centers, mortality for newborns and infants is 10 to 15 percent. Actuarial survival after surgical valvotomy is 87 percent at 10 years and 82 percent at 20 years, with a late mortality risk at 0.4 percent per year for patients with significant residual disease. Mortality from reoperation ranges from 0 to 18 percent (mean 12%), with an actuarial probability of reoperation of 19 percent at 15 years, and 35 percent at 20 years. Restenosis is more frequent after surgery in infancy. Surgery does not prevent endocarditis and valve incompetence is induced in 40 to 50 percent of patients. Balloon dilation is offered as initial palliation in patients with no more than mild regurgitation and peak-to-peak gradients of 50 mmHg or more. Average gradient relief is 50 to 65 percent (100 mmHg, to 25-40 mmHg). Short-term follow-up (2 years) has noted no restenosis or worsening of regurgitation. Hemodynamic and clinical improvement can also be achieved in the neonate, with a low mortality and morbidity. In this setting, concern over femoral artery complications (thrombosis, avulsion, etc.) has prompted other technical avenues of catheter entry including the umbilical, transatrial (transvenous) or carotid artery with excellent hemodynamic results.

Dilation of Bioprosthetic Valves

Bioprosthetic valves (bovine or porcine) have a high failure rate in children and adolescents of > 40 percent at 3 to 5 years after implantation. Valve failure is characterized by calcification of the commissures and within leaflets, often with leaflet tears and ulcerations. Case reports of balloon dilation of such valves have resulted in an average 40 percent, gradient reduction with increased valve incompetence in the majority. In selected cases, reduction in gradient can defer surgery until an adult-sized implantation can be achieved.

CLOSURE OF EXTRACARDIAC AND INTRACARDIAC COMMUNICATIONS

Materials

Transcatheter closure of cardiovascular communications can be accomplished with implantation of occluding devices or materials to promote clot formation, with subsequent ingrowth of fibrous tissue. A variety of embolization materials are available.

Ethanol, acrylates small particles of polyvinyl alcohol are used to obliterate arteriolar end-arteries with diameters < 2 mm. Ethanol (96%) causes immediate vascular occlusion, dehydration, and necrosis, while tissue adhesives form an instant spongy plug upon injection into the target vessels. Care must be taken to avoid malembolization into nontargeted vessels by overflow. Polyvinyl alcohol sponge particles are flushed selectively through wedge catheters into the target vessels. They do not result in permanent occlusion and can be resorbed, and as such are mainly used for temporary flow control, protecting vulnerable beds needing embolization.

Detachable Balloons

Detachable silicone balloons with various diameters (2-9 mm inflated) can be delivered while attached to 2- or 3-Fr catheters through guide delivery systems. The balloons are flow-directed to the target and are inflated with isotonic contrast material where the balloons eventually become embedded in fibrous tissue. If premature deflation occurs, the balloon can migrate distally. If inflation is sustained for >10 days, permanent occlusion occurs in 90 percent of vessels.

Ivalon Plus for Occlusion of the Patent Ductus Arteriosus

Transfemoral closure of the ductus arteriosus can be accomplished with a conical plug of Ivalon sponge (polyvinyl alcohol). The plug is precut to be 20 to 40 percent larger than the aortic end of the ductus, allowing it to become securely wedged in the ductal ampulla. The femoral artery must be at least the size of the ductus to accommodate the plug. It is inserted through a sheath and positioned via a wire loop extending from the femoral artery to the femoral vein. The plug, once positioned, is subsequently invaded by fibrous tissue. Due to the size of the introducer system, its application is limited to adolescents and adults. Arterial complication, plug embolization and dislodgment can occur.

Rashkind Double-umbrella Occluder

The double-umbrella Rashkind occluder is made of two opposing spring-loaded polyurethane foam umbrellas, in 12 mm (ductus < 4 mm) and 17 mm (ductus 4 to 8 mm) diameters. The device is folded into a delivery catheter and it is guided to the ductus from a transvenous approach with a long sheath. Complete occlusion is frequent (45% acutely), but small residual shunts require several weeks to months for complete flow obliteration. Residual shunt rate is 6 to 8 percent at 3 years. Einbolization to pulmonary and systemic vessels has been reported, but catheter retrieval is frequently possible. The Rashkind double-umbrella can be used to close ductus in children as small as 6 kg. In the oversized large ductus (> 8 mm) clamshell occluders have been used successfully.

Gianturco Steel Coils

Gianturco coils are helical flexible stainless steels springs wrapped with Dacron strands. The straightened coil can be inserted into i 4-Fr catheter and upon extrusion takes on the helical shape, with diameters of 2, 3, 5, 8, or 12 mm. The chosen coil should be 20 to 40 percent larger than the vessel to be occluded. Thrombosis occurs within 10 mins and eventually the coil is embedded with fibrous tissue. These devices are easy to use, but can malembolize if flow control is not utilized.

Septal Occluders

Modification of the Rashkind ductal occluder concept has evolved into an occluder that can be placed in selected atrial or ventricular defects. The Lock Clamshell device (CardioSeal, NMT Inc., Boston, MA) consists of two opposing Dacron umbrellas that fold in opposite directions. The center spring hinges allow the device to fold back flat on the opposite aspect of the septum around the defect to be closed. Transesophageal echocardiography has been found useful during device placement to visualize the atrial defect. The device can be used to close defects up to 22 mm in diameter. Placement requires the use of an 11-Fr guide. Experimental studies have found the Dacron fabric to be enmeshed in fibrous tissue, adherent to the septum and endothelialized by 1 month. A single-sided occluder that is positioned against the left atrial septal wall and fixed with a countervailing arm on the right atrial wall is also under clinical investigation as is a nitinol Dacron double-disc design (Angel Wings D, Microvena, Miineapolis, MN).

PROCEDURES

Closure of Aortopulmonary Collaterals

Aortopulmonary collaterals arise, from the aorta and supply parts of the lung, either solely or as a dual supply along with normally connected central pulmonary arteries. These vessels are thin-walled and have segments of stenosis and dilation. Although an additional source of pulmonary blood supply, they complicate surgical repair and post-operative management, by obscuring the surgical field, often requiring circulatory arrest to control flow, impairing myocardial protection, and lowering diastolic pressures. Ligation is recommended at the time of corrective surgery, but can be a technically difficult and time consuming undertaking, and at times impossible from a median stemotomy. A number of centers routinely occlude these vessels immediately pre-operatively with either Gianturco coils or detachable balloons. The vessel must be test-occluded to assure adequate arterial saturations, and angiographic confirmation that the distal lung has central pulmonary artery supply. Complications from the procedure include malembolization into the pulmonary artery with or without pulmonary infarction or other clinical problems. From several reported series, complete occlusion was accomplished in 73 percent, and subtotal or partial occlusion in 25 percent with a 2 percent failure rate. In cyanotic patients, before correction surgery, arterial oxygen saturatioin decreased an average of 5 percent (1 to 15%). An average of three coils (1-8 coils) per vessel were required. Recanalization was found in 10 percent of previously completely occluded vessels while late occlusion can occur in subtotally occluded vessels.

Closure of Arteriovenous Malformations

Systemic and pulmonary arteriovenous malformations can lead to cyanosis and heart failure. These thin walled fistulae are prone to aneurysmal formation and rupture. Surgical approaches consist of local or partial resection of the organ. Transcatheter embolization has been well established as a first line of therapy, particularly in multiple lesions. The complication rate is low. Segmental pulmonary infarctions and embolization have occurred. Using coils and detachable balloons, the feedings vessel can be completely occluded in 80 to 90 percent of cases, with a 13 percent recurrence. In hepatic and pulmonary arteriovenous malformations, feeding vessels frequently reopen or further abnormal vessels recruited.

Closure of Surgical Systemic to Pulmonary Shunts

Surgical shunts that attempt to provide a reliable source of pulmonary blood flow are most often constructed of GoreTex (between the subclavian and pulmonary arteries, and infrequently, from the ascending aorta to Pulmonary artery (central shunt). Transcatheter shunt closure is preferable if closure is the sole indication for surgery or to simplify surgery if arterial saturations can be maintained by another source of pulmonary blood flow. This is particularly true for left sided shunts which are difficult to close surgically. The only complication is malembolization into the pulmonary arteries, which can be retrieved during catheterization. Both coils and balloons have been employed. Distal balloon occlusion during delivery will reduce the rate of malembolization. A Rashkind umbrella can be used in selected instances. In the reported series, 53 percent complete closure was achieved, with subtotal to partial occlusion in 40 percent, and no occlusion in 7 percent. No recanalizations were found on follow-up.

Ventricular Septal Defects

Ventricular defects can lead to congestive heart failure and pulmonary hypertension. Defect size and location can vary and in some may have a muscular or fibrous rim. Closure is recommended for defects with heart failure, pulmonary hypertension, large shunts with failure to thrive, or previous endocarditis. The surgical mortality is low, 2 to 8 percent in infancy and < 1 percent beyond 2 years of age. With apical or multiple muscular defects, surgical mortality is increased, particularly when a left ventriculotomy is required. Long-term follow-up studies have noted that 35 percent of such patients have left ventricular dysfunction. Transcatheter closure was attempted in three children with congenital defects using a Rashkind ductal occluder. Although shunt reduction or complete closure occurred, it was clear that the device design was not appropriate. Subsequently, investigations using the clamshell design in 12 patients[12] have defined this approach useful in selected patients.

Patients with isolated lesions may undergo percutaneous closure as a single procedure, or those with additional defects or lesions requiring surgical repair have the muscular or apical defect closed in the catheterization laboratory pre-operatively.[13] In small infants percutaneous closure may prove impractical (< 4 kgs) therefore a combined surgical approach with device closure placed through the tricuspid valve while on bypass is performed in the operating room.

The Fenestrated Fontan

Ventricular dysfunction, an increased pulmonary vascular resistance, and pulmonary artery distortion contribute to increased mortality after creation of an atrial-dependent pulmonary circulation. Fenestration of the intra-atrial baffle has been suggested to allow maintenance of cardiac output, and although systemic hypoxemia persists, shunting across the fenestration limits increases in right atrial pressure. Subsequent transcatheter closure of the defect can then be undertaken electively if test balloon occlusion of the defect results in acceptable hemodynamics (right atrial mean pressure < 15 mmHg, and maintenance of cardiac output). If the procedure is performed beyond 2 months after surgery, balloon angioplasty of the pulmonary arteries may be undertaken at the same procedure if required.

Endovascular Stents

Various intravascular stent devices have been developed to provide a framework to resist the elastic recoil in vascular stenoses after balloon angioplasty. A variety of designs and materials has been tested in experimental and clinical settings, including a spring-mesh self-expanding stent fitted over a balloon catheter, and temperature-dependent memory metals which expand at body temperatures. The most promising design, with clinical application in children[14] is an expandable stainless steel design mounted on a balloon. The stent is available in three sizes, expandable from 4 to 18 mm. They retain their size and shape after balloon expansion and can be further enlarged with increasing balloon diameters.

Fibrin deposition and subsequent proliferation of neoendothelial cells integrate the stent into the arterial wall. Metal stents protruding into the lumen remain uncovered, and side branches of the stented lumen remain patent. Stented vessels demonstrate medial thinning and intimal proliferation.[15,16] Implantation requires placement of 10- or 11-Fr long sheaths across the stenotic segments for access to the balloon-loaded stent. In the one clinical trial reported,[14] 45 stents were placed in 30 patients, between 0.2 to 30 year old. Twenty-three patients had branch pulmonary artery stenosis. Thirty-six (80%) of the stents were placed successfully and reduced pressure gradients from 50 to 15 mmHg. Five patients had atrial surgery, three obstructed Fontans, one superior vena cava-right atrial junction after sinus venous surgery, and one after a Glenn shunt. Atrial stents reduced pressure gradients from 10 to 2 mmHg. Two stents migrated during implantation and one required surgical removal. Long term anticoagulant or antithrombotic therapy may be required in selected cases.

COMPLICATIONS

Arterial complications are not uncommon after systemic balloon angioplasties or valvuloplasties and have been recorded as high as 45 percent of procedures. Acute thrombosis is most common, and is related to catheter profile and patient size. Infrequently, complete or incomplete disruption or arterial tears can occur. The arterial tear created by catheter insertion results in a hemostatic thrombus which, if large enough, may occlude the vessel. In addition, arterial spasm may lead to stasis of blood and thrombus formation. Presently, use of heparinization protocols or thrombolytic therapy frequently leads to restoration of normal flow. Potential adverse sequelae include decreased growth of the affected limb leading to leg length inequality, vascular insufficiency, and of some importance, loss of arterial access for future diagnostic or interventional procedures. Because balloon intervention for left-sided lesions has only recently (since the mid 1980s) been widely applied, little Iona-term data are present to accurately reflect the incidence of this complication. From the multicenter registry, the incidence of transient pulse loss for aortic balloon valvuloplasties was 12 percent of 204 procedures, 2.5 percent persistent pulse loss (after medical therapy), and 30 percent requiring surgic intervention. Of 141 angioplasties for nativ coarctation of the aorta, 10 percent had arteri complication, 30 percent of which required surgic intervention. Balloon angioplasty for recurrer coarctation reported from the same registr documented 8.5 percent transient pulse loss, 4 percent requiring surgical thrombectomy. A revie of the reported incidence of transient or persister pulse loss by Rothman[17] summarized the acut incidence from a number of centers. The cumulativ incidence of a persistent decrease of absence of le pulses was only 4 percent, although systemati evaluation of pulses was not applied. Transarteri balloon procedures are generally effective and carr a small risk of significant arterial injury. The adven of low-profile catheters and increasing operator skill can lessen the incidence of such problems.

SUMMARY

Catheter therapies have evolved to become importan components in the modalities of therapies used t treat patients with cardiovascular illnesses. Th cumulative experience with balloon dilation o valvular and vascular lesions has demonstrated thei low morbidity and mortality, with short term result similar to surgery. Balloon dilation is the currentl accepted therapy for valvular pulmonary stenosis pulmonary artery stenosis, recurrent coarctation congenital valvular aortic stenosis, and intra-atria baffle obstruction.

Various devices are available for closure of intra- and extra-cardiac lesions. Transcatheter occlusion o aorto-pulmonary collaterals, arteriovenous malformations, and the ductus arteriosus is well established. In selected patients, embolization of surgica shunts is possible. Nonsurgical closure of atrial an ventricular defects has entered clinical trials wit promising early results.

Improvements in existing procedures and implementation of new concepts will solidify the role o catheter therapy for congenital and acquired defects

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Section Four

Metabolic Renal Issues

CHAPTER

Electrolyte Abnormalities in Critically Ill Children

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Problems related to water, sodium, potassium, calcium and magnesium are common in the pediatric intensive care unit as a result of primary illness or as an adverse effect of the therapy. Eitherway, it is important to recognize and look for these abnormalities, to maintain as normal physiological milieu as possible to avoid possible morbidity and mortality associated with these abnormalities.

DISORDERS OF WATER HOMEOSTASIS

Water constitutes 70 and 80 percent of body weight in full term and pretern neonates, respectively, decreasing to 60 percent by 1 year of age. Intracellular fluid constitutes 30 to 40 percent of body weight, while extracellular fluid constitutes 20 to 25 percent of body weight. Extracellular fluid includes plasma (intravascular space, 5 percent body weight), interstitial fluid (15% body weight), and transcellular fluid (pleural, peritoneal, pericardial, and cerebrospinal fluid: 1 to 3 percent body weight).[1]

Two factors determine normal body *water* balance: thirst and ability to concentrate urine. Antidiuretic hormone (ADH) increases resorption of water in the distal collecting tubules, playing a key role in water homeostasis. Osmotic pressure of the extracellular fluid and osmoreceptors in the hypothalamus regulate ADH release, with the threshold for release of ADH being an osmolality of 280 mosm/kg of water. Release of ADH may be initiated or inhibited with changes in plasma osmolality of as little as 1 to 2 percent.[2] Disorders of ADH include diabetes insipidus and the syndrome of inappropriate antidiuretic hormone secretion (SIADH).

Diabetes Insipidus

Diabetes insipidus constitutes a large number of disorders (Table 61.1) having hypovolemic hypernatremia with hypotonic polyuria. Urine osmolality is usually less than 200 mosm/L; plasma osmolality is normal or increased. The most common causes of central diabetes insipidus in the pediatric ICU are hypoxic ischemic encephalopathy,[3,4] severe head trauma.[2]

The diagnosis of diabetes insipidus should be suspected if a polyuric patient has a normal or increased plasma osmolality with urine that is hypotonic compared with plasma. Diabetes insipidus needs to be differentiated from conditions with

Table 61.1: Common causes of diabetes insipidus in the pediatric ICU

Central DI(vasopressin sensitive)*
- Anoxic encephalopathy
- Guillain Barre syndrome
- Suprasellar tumor, cysts
- Postinfectious
- Encephalitis
- Meningitis
- Trauma-basal skull fracture
- Surgical damage to pituitary gland
- Vascular Lesions
- Aneurysm
- Thrombosis

Nephrogenic DI (vasopressin insensitive)*
- ATN** (recovery phase)
- Postobstructive diuresis
- Massive diuretic therapy

*DI=diabetes insipidus;
**ATN=acute tubular necrosis.

excessive fluid intake (hypoosmolar plasma with hypotonic polyuria) and osmotic diuresis (urine osmolarity equal or exceeding that of plasma) induced by mannitol or a high serum glucose value.

Management of Diabetes Insipidus

The first step in managing diabetes insipidus is to replace fluid deficits with isotonic solutions. Ongoing losses should be replaced with solutions not exceeding 30 to 70 mmol/L of sodium. Hyperglycemia needs to be avoided to prevent osmotic diuresis. Intravenous infusion of arginine vasopressin (AVP) is the treatment of choice.[5] The recommended initial starting dose is 0.5 mU/kg/hr. The infusion rate should be doubled every 30 mins (maximum dose 10 mU/kg/hr) to achieve a urine osmolality of at least double that of plasma and to establish a urine output of < 2 mL/kg/hr. Renal failure, profound lactic acidosis, and skin infarction may result from tissue ischemia caused by vasoconstriction from AVP. The synthetic analog of AVP, 1-desamino 8-D-arginine vasopressin (DDAVP), is not commonly used in pediatric ICUs because of its longer half-life.[6]

Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

The most common cause of childhood euvolemic hyponatremia is SIADH, which causes hyponatremia due to water retention from excessive ADH activity with continued sodium excretion. The urine osmolarity is inappropriately high for the serum sodium concentration. Urinary sodium is greater than 20 mmol/L. SIADH occurs most frequently in children with infections involving the central nervous system[7] and during the postoperative period in the pediatric ICU.[8] Other common causes include head injury,[9] respiratory infections,[10] burns,[11] cardiac surgery,[12] and chemotherapy (vincristine)[13] (Table 61.2). Patients with hypothyroidism,[14] adrenal insufficiency, or renal tubular dysfunction may be misdiagnosed as having SIADH. Diuretic therapy may also cause excessive urinary sodium losses with resultant hyponatremia. *Cerebral salt wasting syndrome* has been increasingly recognized in the setting of injury to the central nervous system (CNS) and chronic CNS involvement. Typically patient loses more sodium in the urine and is dehydrated rather than fluid overloaded as in SIADH, requiring more salt, fluid and even floudrocortisone in resistant cases.

Table 61.2: Disorders associated with syndrome of inappropriate diuretic hormone secretion in the pediatric ICU

Central Nervous System
- Infection
- Bacterial meningitis
- Encephalitis
- Trauma
- Tumor
- Guillain Barre syndrome
- Ventriculoatrial shunt malfunction
- Subaracimoid hemorrhage
- Vasculitis

Pulmonary
- Pneumonia
- Bacterial empyema
- Pneumothorax
- Asthma
- Cystic fibrosis
- Malignancy

Cardiac
- Congestive heart failure
- Constrictive pericarditis

Hepatic
- Hepatic failure
- Portal hypertension
- Infections/Sepsis: bacterial, viral

Surgery/Anesthesia
- Postoperative pain
- Peritoneal manipulation

Drugs
- Acetaminophen
- Barbiturates
- Carbamazepine
- Isoproterenol
- Morphine
- Vincristine

Management of SIADH

The underlying condition needs to be treated. Fluid restriction to 50 percent maintenance requirement will increase the serum sodium to normal values in most patients. If hyponatremia is symptomatic or if the serum sodium concentration is < 120 mmol/L, 3 percent saline (0.513 mmol/L of sodium/mL) may be given to correct serum sodium to a conservative target of 125 mmol/L. The millimoles of necessary sodium can be calculated as follows: sodium needed 0.6 × weight (kg) × (125-sodium measured).

An alternative method to managing SIADH is to use furosemide[15] with hourly measurements of urinary sodium and potassium, and replacement with 3 percent saline and potassium chloride until the desired serum value of sodium is achieved. This method causes free water loss via the kidneys and replaces the obligatory sodium and potassium loss, thus achieving normal serum sodium and potassium.

Sodium

The major cation of the extracellular fluid is sodium, with concentration in the extracellular fluid generally maintained in the range of 135 to 140 mmol/ L. Intracellular fluid contains about 10 mmol/L of sodium. The sodium content of the fetus is higher than that of the adult, with the exchangeable pool of sodium being twice as large in the fetus as compared with that pool in adults.[1] The sodium-potassium-activated pump helps to maintain low intracellular sodium. Sodium is important in maintaining cell turgor, intravascular volume, and nerve action potential, therefore affecting almost all the organ systems in the body.

Hyponatremia (Serum Sodium < 135 mmol/L)

Hyponatremia most commonly results from an abnormality in the handling of water.[16] Loss of sodium in excess of water, loss of sodium and water (Gastroenteritis, cerebral salt wasting), water retention (excessive ADH in SIADH), or excess water administration (hypotonic fluids). The most common cause of hyponatremia in the pediatric ICU is SIADH.[17]

Other common causes of hyponatremia in the pediatric ICU include congestive heart failure, excessive loss (renal, gastrointestinal (GI), tube drainage) with hypotonic fluid replacement, third-space losses, and fluid overload[18,19] (Table 61.3).

Ficticious hyponatremia is caused by a redistribution of water between extracellular fluid and intracellular fluid caused by addition of glucose or mannitol to extracellular fluid, which draws free water into extracellular fluid by osmotic gradient. Diabetes mellitus is the leading cause of factitious hyponatremia in children.[19] True serum sodium can be estimated by adding 1.6 mmol/L of sodium for every 100 mg/dL (5.6 mmol/L) increase of blood glucose over normal. Pseudohyponatremia occurs commonly with nephrotic syndrome due to hyperlipidemia because lipids occupy a certain volume of serum water, leading to inaccurate serum sodium measurements. The clinical picture (Table 61.4) depends on the primary condition causing hyponatremia; signs of hypovolemia and dehydration, or fluid overload and edema. Serum sodium concentration of <125 mmol/L may lead to seizures and coma.[16,19] Cerebral salt wasting in acute CNS injury needs to be distinguished from SIADH.[20]

Table 61.3: Causes of hyponatremia in pediatric ICU patients

Euvolemic Hyponatremia
- Iatrogenic
- Parenteral therapy
- SIADH

Hypovolemic hyponatremia
- Factitious: DKA
- Gastrointestinal Losses
- Diarrhea
- Fistula
- Tube drainage
- Third space losses
- Burns
- Muscle trauma
- Peritonitis
- Chest tube drainage
- Renal
- Diuretic phase of ATN
- Postobstructive diuresis
- Renal tubular acidosis
- Diuretic therapy

Hypervolemic hyponatremia
- Congestive heart failure
- Nephrotic syndrome
- Hepatic failure
- Acute renal failure
- Inappropriate dilution of formula
- Mist tent
- Parenteral therapy

SIADH = Syndrome of inappropriate antidiuretic hormone secretion
DKA=Diabetic ketoacidosis
ATN=Acute tubular necrosis

Management of Hyponatremia (Flow chart 61.1)

Regardless of the underlying etiology, the acute treatment of hyponatremic patients with 3 percent saline needs to be considered when the serum sodium concentration is < 120 mmol/L or the patient is symptomatic, i.e. seizures and lethargy. Further

Table 61.4: Clinical manifestations of hyponatremia and hypernatremia

Hyponatremia

- Apathy
- Nausea
- Vomiting
- Ataxia
- Lethargy
- Seizures
- Coma
- Poor Perfusion
- Hypotension
- Edema, if fluid overload

Hypernatremia

- Irritability
- Thirst
- Vomiting
- Fever
- Central nervous system bleeding
- Lethargy
- Seizures
- Coma
- Doughy skin
- Tonic spasm
- Hypotension (late)

therapy depends on whether the patient is hypovolemic, euvolemic, or hypervolemic. Hypovolemia should be corrected first with a 20-mL/kg isotonic saline fluids bolus. After the serum sodium concentration has been corrected to approximately 125 mmol/L, the rest of the sodium deficit should be replaced over 18 to 36 hours with a volume of fluid to be given determined on the basis of the water deficit. Water deficit in child can be calculated on the basis of percent of weight loss, or estimated percent of dehydration (10% dehydration in a 10-kg child would mean a water deficit of 1000 mL). SIADH the most common cause of euvolemic hyponatremia in the pediatric ICU, is treated by fluid restriction. Hypovolemic hyponatremia, secondary to congestive heart failure, nephrotic syndrome, or acute renal failure, requires treatment of the basic disease in addition of fluid restriction and close monitoring of the fluid intake and output.

Hypernatremia (Serum Sodium >150 mmol/L)

The essential pathophysiologic disturbance with hypernatremia is a relative increase in the amount of sodium in the extracellular fluid, as compared with the amount of water in this space. Depending on the patient volume status, three clinical categories of hypernatremia—*euvolemic, hypovolemic* and *hypervolemic* are recognized (Table 61.5).

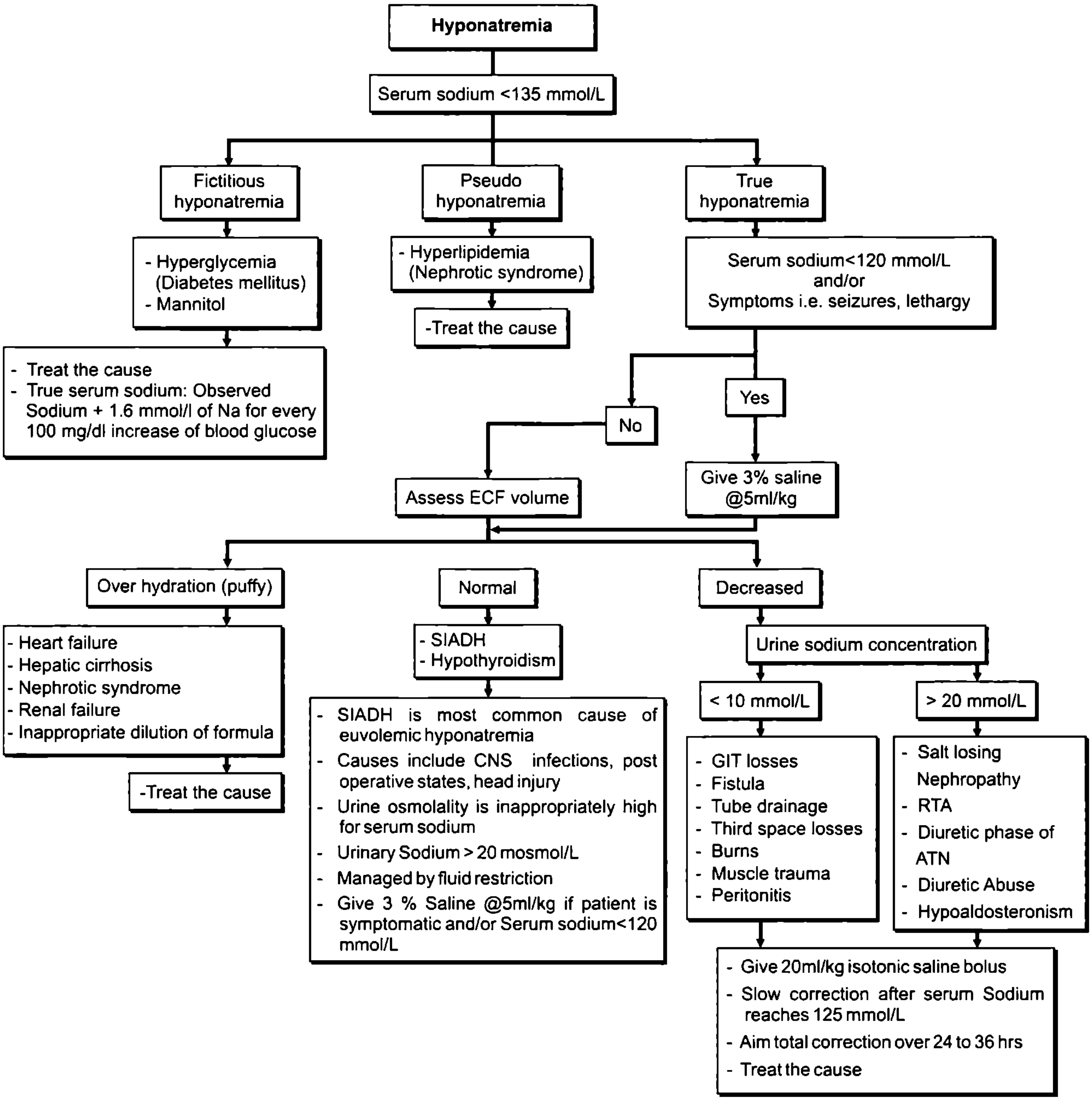
Euvolemic hypernatremia is caused by the intake of excessive amounts of sodium. Sources include inadvertent use of salt rather than sugar in preparing formula[25] excess sodium containing IV fluids, sodium bicarbonate infusion, arterial catheter infusion with heparinized saline, antibiotics, improper fluids for hemodialysis and peritoneal dialysis, and exchange transfusion in preterm neonates.[22-26] A decrease in the glomerular filtration rate contributes to the persistence of the hypernatremic state.

Other important causes include:

Hypovolemic hypernatremia is caused by loss of hypotonic fluid or free-water loss. Over 90 percent of hypovolemic hypernatremia in infants < 2 years is caused by diarrheal illnesses.[23] Other causes include improper dilution leading to feeding of concentrated formula,[21-24] osmotic diuresis (diabetes mellitus), diabetes insipidus, child abuse (enforced thirst, lack of feeding), increased insensible losses, and absence of thirst.[25] Hypervolemic hypernatremia is rare, and is most commonly iatrogenic or accidental. The inadvertent use of intravenous hypertonic solution in a volume expanded patient, and the use of inappropriate dialysis solutions in patients with chronic renal failure are known examples.[26] Primary hyperaldosteronism or Cushing's syndrome may rarely cause hypervolemic hypernatremia.

Clinical Manifestations

Intracellular dehydration is responsible for major central nervous system and hemodynamic manifestations (Table 61.4). With increased osmolality of > 335 mosm/kg, the frequency of intraparenchymal bleeding and venous thrombosis[27] increases, leading to progressive neurologic dysfunction (lethargy, seizures, and coma). Hypotension is a late phenomenon, since intracellular fluid tends to shift to extracellular fluid to maintain the circulating blood volume until severe intracellular dehydration occurs followed by hemodynamic instability. Rhabdomyolysis has also been reported with severe hypernatremia.[28]



Flow chart 61.1: Hyponatremia

Hyponatremia
Serum sodium <135 mmol/L
Fictitious hyponatremia
Pseudo hyponatremia
True hyponatremia
- Hyperglycemia (Diabetes mellitus)
- Mannitol
- Hyperlipidemia (Nephrotic syndrome)
-Treat the cause
Serum sodium<120 mmol/L and/or Symptoms i.e. seizures, lethargy
- Treat the cause
- True serum sodium: Observed Sodium + 1.6 mmol/l of Na for every 100 mg/dl increase of blood glucose
Yes
No
Assess ECF volume
Give 3% saline @5ml/kg
Over hydration (puffy)
Normal
Decreased
- Heart failure
- Hepatic cirrhosis
- Nephrotic syndrome
- Renal failure
- Inappropriate dilution of formula
-Treat the cause
- SIADH
- Hypothyroidism
- SIADH is most common cause of euvolemic hyponatremia
- Causes include CNS infections, post operative states, head injury
- Urine osmolality is inappropriately high for serum sodium
- Urinary Sodium > 20 mosmol/L
- Managed by fluid restriction
- Give 3 % Saline @5ml/kg if patient is symptomatic and/or Serum sodium<120 mmol/L
Urine sodium concentration
< 10 mmol/L
> 20 mmol/L
- GIT losses
- Fistula
- Tube drainage
- Third space losses
- Burns
- Muscle trauma
- Peritonitis
- Salt losing Nephropathy
- RTA
- Diuretic phase of ATN
- Diuretic Abuse
- Hypoaldosteronism
- Give 20ml/kg isotonic saline bolus
- Slow correction after serum Sodium reaches 125 mmol/L
- Aim total correction over 24 to 36 hrs
- Treat the cause

Table 61.5: Causes of hypernatremia in pediatric ICU patients

Euvolemic Hypernatremia
- Exchange transfusion
- Peritoneal or hemodialysis

Hypovolemic Hypernatremia
- Child abuse
- Diabetes insipidus: central or nephrogenic
- Diabetesmellitus
- Gastroenteritis: viral or bacterial
- Hypertonic enemas
- Increased insensible water loss
- Burns
- Phototherapy
- Osmotic diuresis
- Cystic fibrosis

Hypervolemic Hypernatremia
- Hypertonic salt solutions
- Steroid excess
- Sea water drowning

Management of Hypernatremia (Flow chart 61.2)

Any oral or parenteral sources of excess sodium should be discontinued. The underlying disease needs to be treated with appropriate therapy, i.e. AVP for central diabetes insipidus. If the serum sodium concentration is > 200 mmol/L, rapid decrease of the serum sodium value to concentrations of 165 to 170 mmol/L should be considered to prevent permanent neurologic damage. Urgent dialysis is indicated. One may attempt administration of furosemide with hypotonic solutions. Once the serum sodium concentration is down to 160 mmol/L, the remaining water deficit should be replaced slowly over 48 to 72 hours, with continued maintenance fluid therapy.

The water deficit can be calculated as follows:

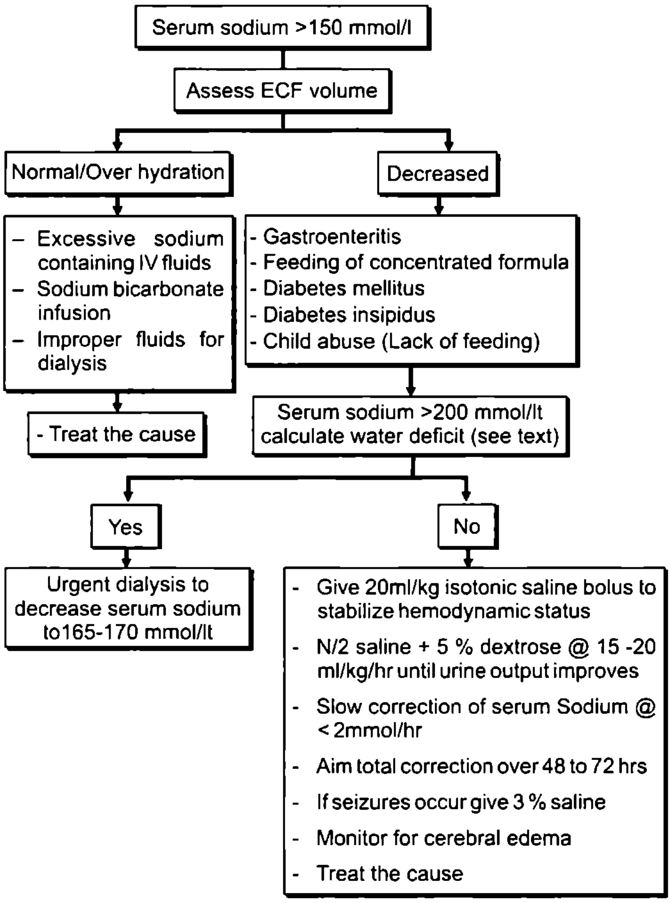
Water deficit in liters = 0.6 x weight in kg x (1-current sodium/140).

The hemodynamic status should first be stabilized with a 10 to 20 mL/kg bolus of normal saline, ringers lactate or 5 percent albumin. Once intravascular volume has been restored, 5 percent dextrose with half-normal saline at 15 to 20 ml/kg/hr may be used until urine output improves. If hypernatremia is longstanding, seizures may occur if the serum sodium concentration is allowed to decrease > 2 mmol/hr, because of rebound osmotic fluid shifts in the central nervous system, causing cerebral edema.[16] Therefore, the serum sodium concentration should be monitored every 4 hours to ensure a satisfactory rate of decrease (approximately 1 mmol/hr) until the serum sodium concentration has decreased to 145 to 150 mmol/ L. The most commonly used solution in the pediatric ICU, for slow correction of hypernatremia, is 5 percent dextrose in quarter-normal saline. Occasionally, quarter-normal saline with 2.5 percent dextrose may be needed because of concomitant hyperglycemia. The serum calcium concentration should also be monitored, since hypocalcemia is frequently present in patients with hypernatremia. The mechanism of the hypocalcemia is unclear.

POTASSIUM DISORDERS

The major intracellular cation is potassium, with the intracellular concentration of potassium being 150 mmol/ L, while the extracellular concentration of

Flow chart 61.2: Hypernatremia


Serum sodium >150 mmol/l
Assess ECF volume
Normal/Over hydration
Decreased
– Excessive sodium containing IV fluids
– Sodium bicarbonate infusion
– Improper fluids for dialysis
- Gastroenteritis
- Feeding of concentrated formula
- Diabetes mellitus
- Diabetes insipidus
- Child abuse (Lack of feeding)
- Treat the cause
Serum sodium >200 mmol/lt calculate water deficit (see text)
Yes
No
Urgent dialysis to decrease serum sodium to165-170 mmol/lt
- Give 20ml/kg isotonic saline bolus to stabilize hemodynamic status
- N/2 saline + 5 % dextrose @ 15 -20 ml/kg/hr until urine output improves
- Slow correction of serum Sodium @ < 2mmol/hr
- Aim total correction over 48 to 72 hrs
- If seizures occur give 3 % saline
- Monitor for cerebral edema
- Treat the cause

potassium is 3.5 to 5 mmol/L.[1] Several factors affect distal tubular potassium secretion, including mineralocorticoid activity, potassium intake, acid base status, urine flow rate, and sodium delivery to the distal nephron. Acidosis shifts potassium outside the cells and insulin shifts potassium into the cell.

Hypokalemia
(Serum Potassium < 3.5 mmoles/L)

A variety of clinical conditions may lead to hypokalemia (Table 61.6). A low serum potassium concentration may result from decreased potassium intake, increased potassium losses (renal or GI), shift of potassium from extracellular fluid to intracellular fluid caused by changes in acid-base status,[29] insulin,[30] beta-adrenergic receptor agonists, epinephrine,[31] and hypothermia.[32] Increased losses may be caused by vomiting, diarrhea, colostomy, or nasogastric suction. Excessive renal losses of potassium may be caused by prolonged diuretic therapy, magnesium deficiency, glucocorticoids (Cushing's syndrome), mineralocorticoids (hyperaldosteronism, adrenogenital syndrome), high renin states (such as renal artery stenosis), aminoglycosides, amphotericin, cisplatin, carbenicillin, ticarcillin, Bartter's syndrome, Fanconi's syndrome, and renal tubular acidosis.[33] Factors affecting shifts of potassium across the cell membrane may change the ratio of intracellular-to-extracellular potassium. Acute metabolic alkalosis increases cellular influx of potassium (for each 0.1 unit increase in pH the serum potassium concentration decreases by 0.2 to 0.4 mmol/L). Chronic metabolic alkalosis increases potassium losses in exchange for hydrogen ions at the renal level. Chronic respiratory alkalosis has minimal or no effect on serum potassium. Insulin, beta-adrenergic receptor agonists (albuterol, terbutaline), and hypothermia lead to a shift of potassium into cells, causing hypokalemia. The relationship between the serum potassium concentration and total body potassium content has no definite correlation, and currently, there is no readily available method of determining total body potassium loss.

Table 61.6: Common causes of hypokalemia in pediatric ICU patients

Decreased intake/Gastrointestinal losses
- Vomiting
- Diarrhea
- Colostomy
- Nasogastric drainage

Renal Losses
- Diuretics
- Tubular diseases
- Cushing's syndrome
- Hypomagnesemia
- Hyperaldosteronism
- Aminoglycosides
- Amphotericin
- Ticarcillin

Ionic Shift
- Insulin
- Epinephrine
- Beta stimulants
- Metabolic alkalosis
- Hypothermia

Clinical Manifestations

With hypokalemia, the ratio of intracellular-to-extracellular potassium is increased, which interferes with neuronal impulse formation, propagation, and muscle contraction. Muscle weakness, intestinal ileus, and gastric dilation occur first. If hypokalemia is persistent, electro-cardiogram (ECG) abnormalities may occur, including T-wave flattening or inversion, and/or the appearance of a U-wave. Prolonged hypokalemia may lead to nephrosclerosis and renal interstitial fibrosis, resulting in systemic alkalosis caused by increased hydrogen ion secretion into the urine.[34] In patients with liver failure, hypokalemia can worsen hepatic encephalopathy by increasing the production of ammonia in the renal cortex.[35]

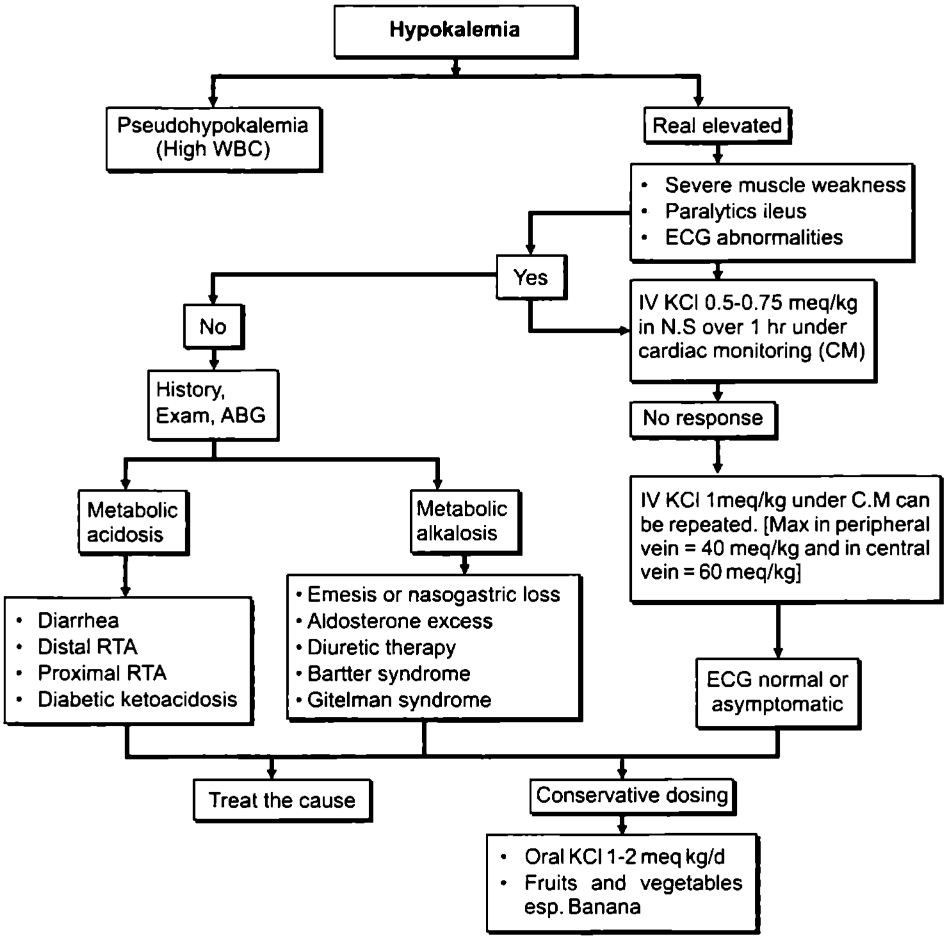
Management of Hypokalemia (Flow chart 61.3)

Underlying condition needs to be treated in addition to correction of the acid-base status and accompanying electrolyte abnormalities, i.e. hypercalcemia and hypomagnesemia. If hypokalemia is caused by diuretics, potassium supplements may be used in addition to potassium sparing diuretics (spironolactone). Ongoing potassium losses (GI or renal) need to be measured and replaced, either enterally or intravenously. Potassium chloride is the preferable salt since it replenishes chloride and corrects the alkalosis associated with hypokalemia. Hypokalemia may enhance digitalis toxicity, especially in patients with congestive heart failure or if there is coexisting hypercalcemia or hypomagnesemia. Potassium boluses should be avoided in patients with mild hypokalemia. If serum potassium concentration is < 2.5 mmol/L, a dose of 0.5 mEq/kg of potassium chloride infused over 30 mins with continuous ECG monitoring may be safely used in children, except in the settings of shock, oliguria, or acidosis. Potassium chloride should not be pushed intravenously due to risk of ventricular fibrillation. Patients with diabetic ketoacidosis should get adequate potassium chloride and potassium phosphate (usually 20 mEq/L of each salt) to prevent the hypokalemia and phosphate depletion, which usually accompanies the disease.

Hyperkalemia (Serum Potassium > 5 mmoles/L)

Hyperkalemia is a life-threatening emergency that is most often seen in the pediatric ICU in the setting of decreased renal function (Table 61.7). Other causes include increased potassium intake,[36] excessive endogenous release, i.e. extensive burns, major trauma, massive hemolysis, or a shift of intracellular potassium to extracellular fluid. Organic acidoses have minimal or no effect on the serum potassium concentration. Diabetic ketoacidosis causes hyperkalemia due to insulin deficiency, resulting in efflux of potassium from cells.[37] Capillary blood samples in neonates may show falsely increased potassium concentrations caused by hemolysis that is induced by squeezing the heel of the neonate's foot to obtain blood.

Flow chart 61.3: Hypokalemia


Hypokalemia
Pseudohypokalemia (High WBC)
Real elevated
• Severe muscle weakness
• Paralytics ileus
• ECG abnormalities
Yes
No
IV KCl 0.5-0.75 meq/kg in N.S over 1 hr under cardiac monitoring (CM)
No response
IV KCl 1meq/kg under C.M can be repeated. [Max in peripheral vein = 40 meq/kg and in central vein = 60 meq/kg]
ECG normal or asymptomatic
History, Exam, ABG
Metabolic acidosis
Metabolic alkalosis
• Diarrhea
• Distal RTA
• Proximal RTA
• Diabetic ketoacidosis
• Emesis or nasogastric loss
• Aldosterone excess
• Diuretic therapy
• Bartter syndrome
• Gitelman syndrome
Treat the cause
Conservative dosing
• Oral KCl 1-2 meq kg/d
• Fruits and vegetables esp. Banana

RTA : Renal tubular acidosis
ABG : Arterial blood gas

Table 61.7: Common causes of hyperkalemia

Impaired Renal Excretion
- Renal failure
- Adrenal insufficiency

Increased Intake
- Penicillin potassium salts

Iatrogenic
- Intravenous fluids
- Stored blood, platelet transfusion
- Endogenous Potassium Release
- Rhabdomyolysis: trauma, heat stroke
- Extensive burns
- Tumor lysis syndrome
- Severe rapid hemolysis
- Hemolytic uremic syndrome
- Succinylcholine

Ionic Shift
- Metabolic acidosis

Drugs
- Glucose
- Mannitol

Digitalis Overdose
- Alfa agonists
- Beta-blockers
- Ace inhibitors
- Nonsteroidal anti-inflammatory agents
- Potassium-sparing diuretics

Miscellaneous
- Spurious hyperkalemia
- Difficult blood drawing (hemolysis)
- Thrombocytosis

Succinylcholine,[38] commonly used for facilitating endotracheal intubation in pediatric ICU patients, may cause hyperkalemia, leading to fatal ECG abnormalities, including ventricular fibrillation and cardiac arrest, especially if used in patients with burns, massive tissue injury, renal failure, paraplegia, or muscle dystrophy. Non depolarising muscle-relaxants such as atracurium, vecuronium, or rocuronium should be used. Nonsteroidal anti-inflammatory drugs, such as indomethacin, may decrease distal tubular flow and renin release, leading to decreased potassium excretion and hyperkalemia. Captopril inhibits aldosterone biosynthesis and results in hyperkalemia. Propranolol inhibits renin release and decreases aldosterone biosynthesis, while adrenergic receptor agonists, i.e. phenylephrine cause potassium efflux from cells. Both drugs can cause clinically important hyperkalemia in patients with renal failure,[39] Digitalis toxicity may cause severe hyperkalemia.[40]

Clinical Manifestations

An increased serum potassium concentration affects the transmembrane potential, leading to delayed depolarization, faster repolarization, and a slowing of nerve conduction velocity. Initially, paresthesia, and, later, muscle weakness may eventually lead to flaccid paralysis. The ECG typically shows peaked T-waves, lengthening of the PR interval, and widening of the QRS complex, which may progress to ventricular fibrillation if not treated immediately. These ECG changes, if seen in a child with renal failure, should be presumed to be caused by hyperkalemia until proven otherwise. If cardiac arrest occurs in a patient with renal failure, hyperkalemia should be strongly considered as a possible cause and intravenous calcium chloride given.

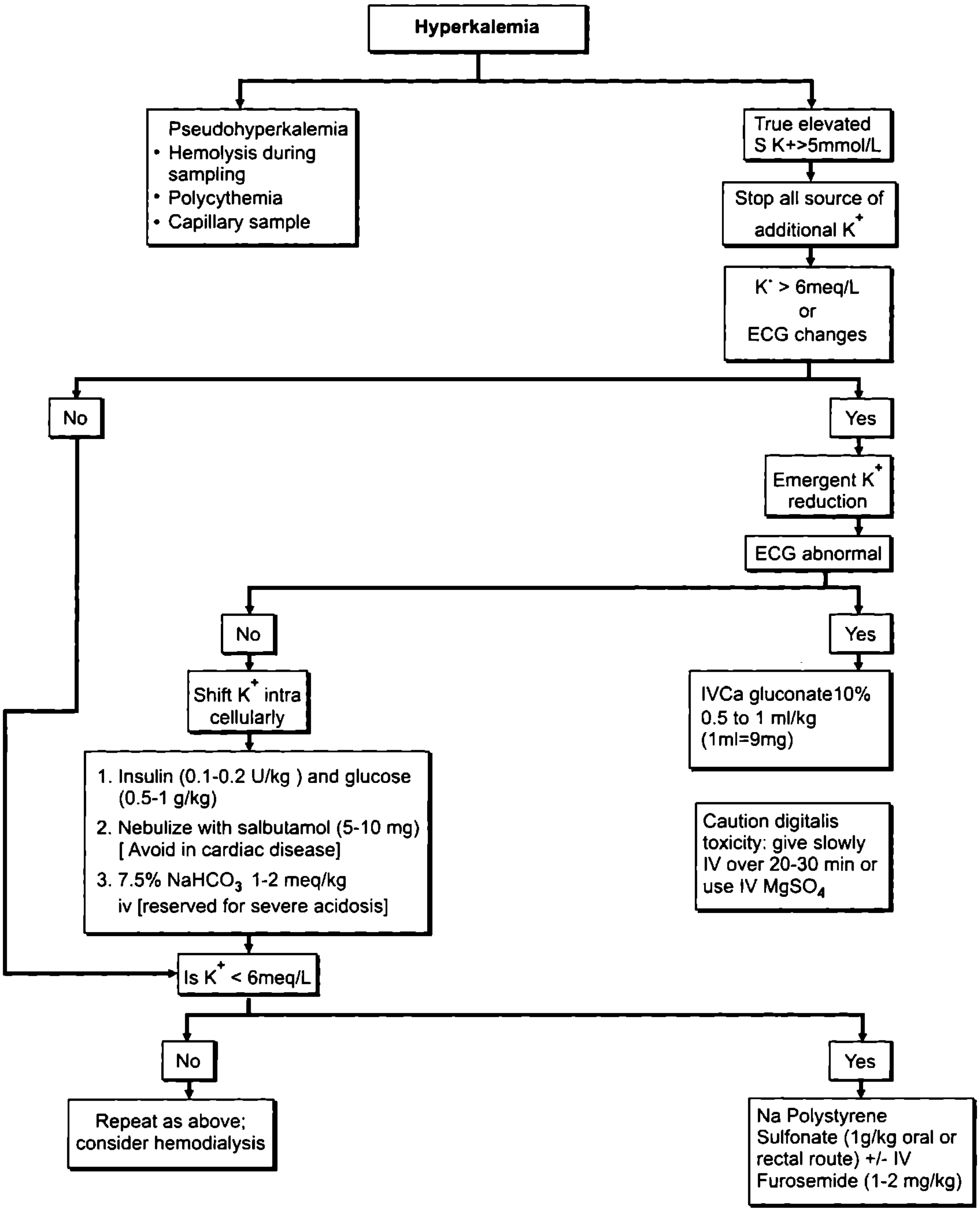
Management of Hyperkalemia (Flow chart 61.4)

Hyperkalemia with relatively mild ECG changes, such as peaked T-waves, may be treated with intravenous sodium bicarbonate (1 to 2 mmol/ kg over 15 to 30 mins). If a widened QRS complex is present, intravenous 10 percent calcium chloride (0.25 mL/kg over 5 to 10 mins); or calcium gluconate (0.5 -1 mL/kg IV) with ECG monitoring should be given immediately. Intravenous glucose (0.5 to 1.0 g/kg) and insulin (0.1 to 0.2 u/kg) may also be used to shift extracellular potassium into cells. These measures, however, do not result in net potassium removal. Sodium polystyrene sulfonate (1 gm/ kg by mouth or by rectal enema), which is an ion exchange resin, exchanges sodium for potassium and is more effective than bicarbonate, glucose, and calcium for removing potassium. Sodium polystyrene sulfonate may cause sodium retention and fecal impaction. All of these measures are helpful until a more definitive therapeutic modality can be initiated, such as peritoneal or hemodialysis, especially if the underlying problem is renal failure, massive hemolysis, burns, or crush injury.

CALCIUM DISORDERS

Bones contain 99 percent of the body's calcium.[1] Serum parathyroid hormone and vitamin D regulate the ionized calcium concentration in serum by mobilizing calcium from the bone and increasing calcium resorption.

Flow chart 61.4: Hyperkalemia



Hyperkalemia
Pseudohyperkalemia
• Hemolysis during sampling
• Polycythemia
• Capillary sample
True elevated S K+>5mmol/L
Stop all source of additional K^+
K^+ > 6meq/L or ECG changes
No
Yes
Emergent K^+ reduction
ECG abnormal
No
Yes
Shift K^+ intra cellularly
1. Insulin (0.1-0.2 U/kg) and glucose (0.5-1 g/kg)
2. Nebulize with salbutamol (5-10 mg) [Avoid in cardiac disease]
3. 7.5% $NaHCO_3$ 1-2 meq/kg iv [reserved for severe acidosis]
IVCa gluconate10% 0.5 to 1 ml/kg (1ml=9mg)
Caution digitalis toxicity: give slowly IV over 20-30 min or use IV $MgSO_4$
Is K^+ < 6meq/L
No
Yes
Repeat as above; consider hemodialysis
Na Polystyrene Sulfonate (1g/kg oral or rectal route) +/- IV Furosemide (1-2 mg/kg)

Hypocalcemia

On admission to the pediatric ICU, hypocalcemia is a common problem in critically ill children. In a study done in the pediatric ICU at Massachusetts General Hospital, 49 percent of critically ill children had low total serum calcium values and 18 percent had ionized hypocalcemia.[41] Critically ill adults have been shown to have a similar frequency of hypocalcemia.[42] Low serum albumin concentrations may affect the measurement of total calcium, although ionized calcium may be normal. Similarly, acidosis decreases the protein binding of calcium and increases the ionized fraction of calcium in the serum. A decreased total serum calcium concentration may be associated with normal or lowionized calcium values. However, total serum hypocalcemia is not an accurate predictor of ionized hypocalcemia. Common causes of hypocalcemia in pediatric ICU patients include cardiac surgery requiring cardiopulmonary bypass, use of citrate preserved blood, sepsis, burns, hypomagnesemia, renal failure, loop diuretics, steroid therapy, albumin, and occasionally hypoparathyroidism and vitamin D deficiency (Table 61.8). Citrate-preserved blood causes hypocalcemia due to chelation of free calcium by the citrate anticoagulant. Sepsis is associated with hypocalcemia.[43] The exact mechanism is unclear. One of the mechanisms may be that interleukin-1 (a monokine) may induce an increase in intracellular calcium, which may suppress the parathyroid-hormone response to ionized hypocalcemia and thus maintain ionized hypocalcemia during sepsis.[43]

Table 61.8: Causes of hypocalcemia in pediatric ICU patients

Blood transfusion (chelation)
- Sepsis
- Burns
- Toxic shock syndrome
- Respiratory alkalosis
- Neonatal hypocalcemia
- Hypoparathyroidism
- Post-neck surgery
- DiGeorge syndrome
- Vitamin D deficiency
- Hypomagnesernia
- Hyperphosphatemia

Drugs
- Aminoglycosides
- Glucocorticoids
- Furosemide
- Phenobarbital
- Phenytoin
- Phosphates

Aminoglycosides induce hypomagnesemia,[44] which may, in turn, lead to hypocalcemia secondary to suppression of parathyroid hormone. Glucocorticoids decrease intestinal calcium absorption and increase calciuria. Furosemide causes hypocalcemia by increasing renal calcium excretion. Phenobarbital may decrease 25-hydroxy vitamin D concentrations by induction of microsomal enzymes, leading to hypocalcemia. Hyperphosphatemia caused by tumor lysis, renal failure, and other iatrogenic causes may cause hypocalcemia. After neck surgery, patients may develop hypocalcemia due to vascular ischemia to the parathyroid gland or because of accidental resection of the parathyroid gland. Early or late neonatal hypocalcemia, although generally not seen in the pediatric ICU, may be an important cause of neonatal seizures in the first 2 weeks of life, requiring admission to the pediatric ICU.

Clinical Manifestations

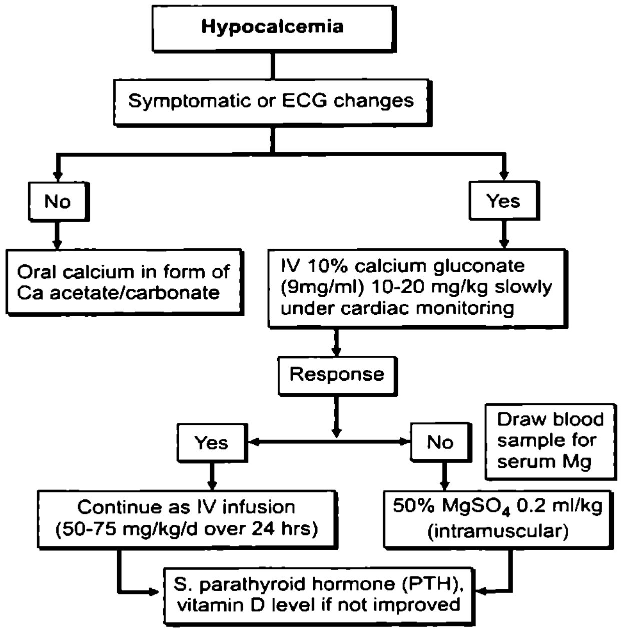
Ionized hypocalcemia may lead to tetany. Respiratory effects of tetany include stridor, laryngospasm and apnea. Neuromuscular effects include muscle cramps, muscle twitching, and carpopedal spasm. Hypocalcemia may result in paresthesias and seizures. Cardiovascular effects of ionized hypocalcemia include hypotension and poor myocardial contractility, catecholamine unresponsiveness, and dysrhythmias including prolonged QT interval, T-wave inversion and bradycardia.

Management of Hypocalcemia (Flow chart 61.5)

Emergency Treatment

Treatment of hypocalcemia may include 0.2 to 0.25 ml/kg of 10 percent calcium chloride given intravenously over 20 mins with continuous ECG monitoring (caution: bradycardia). Alternatively 10% calcium gluconate 0.5-1 ml/kg (20 mEq = 90 mg; 1 ml = 9 mg) may be given. In the absence of an apparent cause for the hypocalcemia, serum magnesium and phosphorus concentrations should be measured. If magnesium concentrations are low,

Flow chart 61.5: Hypocalcemia


Hypocalcemia
Symptomatic or ECG changes
No
Yes
Oral calcium in form of Ca acetate/carbonate
IV 10% calcium gluconate (9mg/ml) 10-20 mg/kg slowly under cardiac monitoring
Response
Yes
No
Draw blood sample for serum Mg
Continue as IV infusion (50-75 mg/kg/d over 24 hrs)
50% MgSO4 0.2 ml/kg (intramuscular)
S. parathyroid hormone (PTH), vitamin D level if not improved

magnesium replacement is indicated. If magnesium and phosphorus concentrations are increased, renal failure should be suspected as a possible cause. If both magnesium and phosphorus concentrations are normal, serum parathyroid hormone should be measured to differentiate hypoparathyroidism from pseudohypoparathyroidism or inadequate vitamin D effect. If manifestations of tetany are caused by hypomagnesemia, calcium therapy alone may not be able to correct the clinical manifestations; magnesium therapy is indicated.

Ionized hypocalcemia is a common problem in critically ill children and is associated with greater severity of illness and mortality.[41] A routine measurement of ionized calcium and calcium replacement therapy to maintain ionized normocalcemia in all critically ill pediatric patients is recommended. It should be understood, however that albumin level, pH and magnesium levels should also be normalized to maintain normocalcemia.

Hypercalcemia

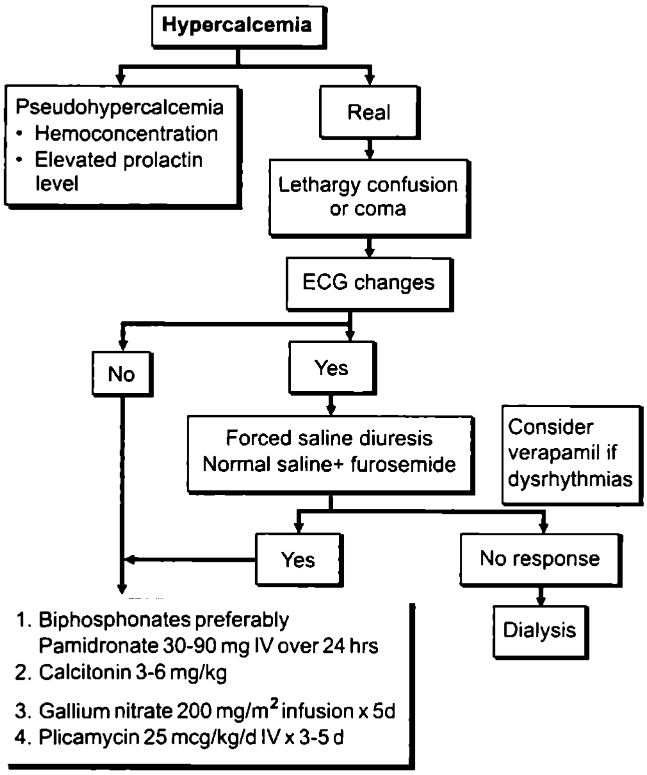
Hypercalcemia is seen relatively infrequently in the pediatric ICU. When seen, the usual causes include immobilization,[45] iatrogenic causes, and malignancies (e.g. neuroblastoma).[46] Hyperparathyroidism is uncommon, but such patients may be seen in the pediatric ICU for postoperative observation after neck exploration and parathyroidectomy.[47] Immobility causes hypercalcemia due to excessive bone resorption. Serum calcium concentrations should be measured in an immobile child with unexplained hypertension. Iatrogenic causes of hypercalcemia include miscalculation of the amount of calcium in hyperalimentation (Parenteral nutrition) solution, hypervitaminosis A or D, and excessive use of calcium-containing antacids (milk alkali syndrome). Pheochromocytoma,[48] Addison's disease, granulomatous disease such as sarcoidosis, familial hypocalciuric hypercalcemia, use of thiazide diuretics, Williams' syndrome[49] (Elfin facies, supravalvular aortic stenosis and mental retardation), include some of the uncommon causes in childhood. Hyperthyroidism causes hypercalcemia by direct effects of thyroid hormone on the skeleton, increasing bone turnover and calcium release.

In most cases of hypercalcemia, a cause can generally be determined by careful history, physical examination, and review of the drug therapy sheet and composition of hyperalimentation solution. Normal blood urea nitrogen, creatinine, and serum phosphorus concentration should rule out a renal cause. Determination of fractional excretion of calcium will be useful for the diagnosis of hypercalciuric syndromes. Serum parathyroid hormone concentrations are increased with primary hyperparathyroidism, but they are normal or decreased with malignancy.

Management of Hypercalcemia (Flow chart 61.6)

The goal of therapy is to minimize calcium intake and increase calcium excretion. General measures consist of discontinuation of calcium-containing fluids, mobilization of the patient, hydration with diuretic therapy to improve calcium excretion, and correction of other electrolyte abnormalities. The administration of normal saline prevents proximal tubular resorption of calcium, while furosemide has a calciuric effect; use of both agents in combination is effective in decreasing serum calcium concentrations. In patients with renal failure, dialysis may be necessary. Drugs decreasing bone resorption of calcium, such as calcitonin, glucocorticoids, and mithramycin, are rarely needed in the pediatric ICU. Chelators, e.g. phosphates and EDTA are indicated

Flow chart 61.6: Hypercalcemia


Hypercalcemia
Pseudohypercalcemia
• Hemoconcentration
• Elevated prolactin level
Real
Lethargy confusion or coma
ECG changes
No
Yes
Forced saline diuresis
Normal saline+ furosemide
Consider verapamil if dysrhythmias
Yes
No response
Dialysis
1. Biphosphonates preferably Pamidronate 30-90 mg IV over 24 hrs
2. Calcitonin 3-6 mg/kg
3. Gallium nitrate 200 mg/m² infusion x 5d
4. Plicamycin 25 mcg/kg/d IV x 3-5 d

for the management of life-threatening hypercalcemic emergencies. The major disadvantage of using chelators is the risk of metastatic calcification. Phosphates should not be used if the patient has hyperphosphatemic hypercalcemia. Calcium antagonists, such as verapamil, may be used in emergency situations with dysrhythmias associated with hypercalcemia.

MAGNESIUM

Magnesium is the fourth most abundant cation in the body[1] and second most common intracellular cation next to potassium. Magnesium has an important role in cellular enzymatic activity, especially glycolysis and the stimulation of adrenosine triphosphatase. In an infant, total-body magnesium amounts to approximately 22 mEq/kg.[1] Less than 1 percent of total body magnesium is found in the serum, and thus, serum concentrations may not accurately reflect intracellular stores.[50] Serum magnesium concentrations normally range from 1.5 to 2 mg/dL (0.6 to 0.8 mmol/L). Approximately 80 percent of circulation magnesium is ultrafilterable and 20 percent is protein bound. Currently, a simple filter method is available for measuring ultrafilterable (ionized plus chelated) magnesium. More recently an ion-selective electrode for measurement of ionized magnesium has become available, making it possible to measure the physiologically active ionized fraction of magnesium. However the importance of routine measurement of ionized magnesium is not yet established as compared to routine measurement of ionized calcium in critically ill children.

Magnesium homeostasis is primarily regulated in the kidney by tubular resorption, which is enhanced by parathyroid hormone, vitamin D, magnesium depletion, hypothyroidism, and hypocalcemia.[51-53] Daily intake of magnesium in children ranges from 10 to 25 meq/day, generally exceeding the minimum requirement of 0.3 mEq/kg/day.

Hypomagnesemia

Decreased intake along with increased GI losses or inadequate renal conservation of magnesium frequently results in hypomagnesemia in pediatric ICU patients (Table 61.9). Very little information is available regarding the incidence of hypomagnesemia in critically ill children. In one study, at least 13 percent of critically ill children admitted to the pediatric ICU at Massachusetts General Hospital had ultrafilterable hypomagnesemia.[54] Studies in the adult ICUs have found 20 to 60 percent of patients to be hypomagnesemic.[55-59] Infants undergoing surgery, who may receive magnesium-free fluids for

Table 61.9: Causes of hypomagnesemia in pediatric ICU patients

- Starvation
- Refeeding after starvation
- Prolonged IV fluid therapy
- Gastrointestinal losies
- Malabsorption
- Renal losses
- Sepsis
- Burns
- Hypothermia
- Aminoglycosides
- Amphotericin
- Digoxin
- Furosemide
- Theophylline

prolonged periods of time in the perioperative period and in the pediatric ICU, may develop hypomagnesemia. Infants with either early or late neonatal tetany often also have hypomagnesemia. Late neonatal tetany may not respond to treatment with calcium until magnesium concentrations have been normalized. Thirty-two percent of all critically ill neonates (preterm and full-term) had ultrafilterable hypomagnesemia on admission to the neonatal ICU at the Massachusetts General Hospital when compared with the normal range in controls.[60,61]

The main cause of hypomagnesemia in the pediatric ICU is inadequate supplementation of magnesium in the critically ill patient receiving no enteral feeds. Excessive GI losses, caused by small bowel disease or resection, prolonged nasogastric suction, colostomy, malabsorption, diarrhea, and laxative use can also lead to magnesium depletion. Increased renal losses may be drug-induced (furosemide, gentamicin,[62] calcium, digoxin, amphotericin B,[63] insulin, and theophylline) or due to intrinsic renal disease. Other conditions leading to excessive renal losses include blood transfusion, cardiopulmonary bypass,[64,65] diabetic ketoacidosis, hypokalemia, hyperparathyroidism, hyperaldosteronism, and hyperthyroidism. Patients with familial hypomagnesemia usually have poor gut absorption.[66] A shift of magnesium from the extracellular fluid to the intracellular fluid may occur when a magnesium-depleted patient (with intracellular magnesium depletion) gets fed after a period of starvation. Increased catecholamines, correction of acidosis, and hungry bone syndromes may also lower serum magnesium values by similar mechanisms.

Clinical Features

The symptoms of hypomagnesemia are primarily related to increased neuromuscular irritability, and include tetany, tremors, and seizures. Personality changes, nausea, anorexia, and muscle weakness may also be seen. Symptomatic children usually have serum magnesium concentrations of < 1 mg/dL (< 0.4 mmol/L). Hypocalcemia or hypokalemia (which commonly accompany hypomagnesemia) may play an important role in producing the symptoms because serum magnesium concentrations seem to have a less consistent relationship with symptoms. Correction of hypomagnesemia can improve respiratory muscle strength, and should be considered in a patient on the ventilator failing to wean due to muscle weakness.[67] The cardiovascular effects of hypomagnesemia include dysrhythmias (prolonged PR and QT interval, ST depression, widening of T-waves, and QRS complexes), digitalis sensitivity, hypertension, and vasospasm. Hypokalemia is frequently associated with hypomagnesemia due to impaired renal potassium conservation.[68] Hypocalcemia accompanying hypomagnesemia occurs due to decreased parathyroid hormone secretion, end-organ resistance to parathyroid hormone, and vitamin D resistance.[69,70]

Management of Hypomagnesemia

The primary cause of hypomagnesemia needs to be treated, i.e. GI loss, renal failure, or malnutrition. Magnesium deficiency is treated by the administration of magnesium supplements. For the patient with normal renal function, up to 1 mEq/kg/day can be added to the maintenance fluid solution, which avoids the highpeak concentrations and reduces the proportion of administered magnesium that is lost in the urine. Serum magnesium concentration should be followed closely, especially in the patient with poor renal function.[71] Magnesium oxide and gluconate are used for enteral replacement; 1 mEq (0.5 mmol) of magnesium is equivalent to 12.3 mg of elemental magnesium. If the serum magnesium concentration is 1 mg (dl < 0.4 mmol/L), magnesium sulfate (50% solution, up to 100 mg/kg-dose) can be intravenously infused slowly or given by the intramuscular route.

Hypermagnesemia

Hypermagnesemia is rarely seen in pediatric ICU patients. When seen, the most common cause is iatrogenic administration, especially in the setting of decreased renal function. In the neonatal ICU, common causes of hypermagnesemia include maternal magnesium sulfate therapy for pregnancy induced hypertension and perinatal asphyxia. Usual sources of a magnesium load include magnesium containing laxatives, enemas, and magnesium-containing intravenous fluids. The symptoms occur when the serum concentration of magnesium is > 5 mg/dL (> 2 mmol/L). Hyporeflexia precedes the respiratory depression, drowsiness, and coma. ECG changes include prolonged PR, QRS, and ST intervals, and bradycardia, leading to hypotension and cardiac arrest [serum magnesium > 15 mg/dL (> 6 mmol/L)]. Hypermagnesemia may increase the duration of action of nondepolarizing muscle relaxants. Intravenous calcium can be given to reverse the neuromuscular and cardiotoxic effects of hypermagnesemia. Definitive therapy to lower the serum magnesium concentration consists of stopping magnesium containing drugs and fluids, followed by the administration of normal saline and furosemide therapy to enhance renal excretion. In patients with renal failure, excess magnesium may have to be removed by dialysis.

SUMMARY

Electrolyte abnormalities are common in critically ill children admitted to the pediatric ICU. Most of the fluid and electrolyte abnormalities in critically ill children can be easily treated once recognized. Such abnormalities should be looked for routinely in all critically ill children. Correction of sodium (hypo or hypernatremia) should be slow to avoid osmotic shifts in the brain so as to prevent siezures and further central nervous system complications. Intravenous pushes of potassium should be avoided even in severe hypokalemia. Hyperkalemia with ventricular dysrhythmias is a medical emergency requiring immediate therapy with intravenous calcium. Administration of calcium, correction of albumin and pH are all important to keep a normal level of ionized calcium in critically ill children. Normal ionized levels of magnesium are probably important, but certainly ongoing hypomagnesemia can be prevented by instituting early feeding in critically ill children, as well as providing maintenance magnesium doses in the intravenous fluids of patients not receiving enteral feeds.

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CHAPTER

Inborn Errors of Metabolism

Vinay K Aggarwal, IC Verma, Nitesh Singhal

Metabolic derangements are frequently encountered in an intensive care unit, and they may be life-threatening. Derangements, such as acidosis and hyperammonemia, are commonly secondary to hypoxia, hypotension, severe sepsis, liver and renal failure, problems that are present in many children admitted to Pediatric ICU. Primary metabolic derangements are seen infrequently, but in order that they are not missed, a high index of suspicion for inborn errors of metabolism (IEM) should be kept. A history of sibling death from a similar problem, consanguinity, sudden onset of symptoms like refusal to feed or tachypnea in an otherwise healthy neonate with no risk factors; and onset of encephalopathy in a young child following a trivial infection should raise suspicions of an inborn error of metabolism.[1] In this chapter emphasis shall be on those metabolic disorders that are seen in the intensive care unit (Table 62.1).

PATHOPHYSIOLOGY

The genetic mutation in the DNA is translated into a metabolic block that may affect catabolism or anabolism of proteins, carbohydrates, fatty acids, nucleic acids, minerals, energy metabolism and components of the respiratory chain. The block may be complete or incomplete due to the different types of mutations in the gene, hence, the clinical presentation of the same disease may be variable. Severe defect presents in the newborn period, whereas milder defect presents later in life- triggered by trivial infections or stress of fasting. Several vitamins act as cofactors in the metabolic pathways and their administration in high-doses may bypass the block.[2]

Table 62.1: Causes of common metabolic diseases with acute onset

I. *Organic Acidemias*
   1. Propionic acidemia
   2. Isovaleric acidemia
   3. Methyl malonic acidemia
   4. Multiple carboxylase deficiency
   5. Lactic acidosis with pyruvate carboxylase deficiency
   6. Pyruvate dehydrogenase deficiency.
   7. Glutaric acidemia

II. *Hyperaminoacidemias*
   1. Maple syrup urine disease
   2. Non-ketotic hyperglycinemia
   3. Homocystinuria

III. *Hyperammonemia*
   1. Carbamyl phosphatase synthetase 1 deficiency (CPS)
   2. Ornithine transcarbamylase deficiency (OTC)
   3. Arginosuccinic acidemia
   4. Citrulinemia
   5. Argininosuccinic and lyase deficiency

IV. *Hypoglycemia*
   1. Galactosemia
   2. Medium chain acyl CoA dehydrogenase deficiency
   3. Glycogen storage disease I, III, and VI
   4. Hereditary fructose intolerance

The usual clinical presentations of IEM are (Flow charts 62.1-62.4):

1. *Hypoglycemia:* Glycogen storage diseases especially type I, disorders of gluconeogenesis, amino acids, organic acids, fatty acids such as medium chain acyl CoA dehydrogenase deficiency can present with hypoglycemia.
2. *Acid-base Imbalance:* Lactic acidosis is commonly secondary to hypoxia, hypotension, and infection. Primary lactic acidosis is very rare. At an early

stage increased anion gap [normal anion gap is 18-20 mmol, $(Na^+K) - (Cl' + HCO_3')$] may indicate accumulation of organic acids such as methylmalonic acid or propionic acid apart from lactic acid.

3. *Encephalopathy:* Neurological dysfunction occurs secondary to accumulation of organic acids, ammonia, and presence of amino acid precursors prior to the metabolic block.[3] If the defect is partial or cofactor dependent child may present late in infancy or in childhood following infection or stress. The possible disorders are those of urea cycle, amino acids, organic acids, electron transport chain (pyruvate dehydrogenase deficiency), and fatty acid oxidation defects.
4. *Liver dysfunction:* Consider galactosemia, tyrosinemia type I, and Wilson's disease. Vomiting and tachypnea may be early symptoms of liver failure.
5. *Others:* Neutropenia, thrombocytopenia, coagulation defects can be features of IEM. Skin manifestations in the form of generalized erythematous rash with exfoliation and alopecia totalis are associated with multiple carboxylase deficiency.

Table 62.2: Useful investigations for IEM (Inborn errors of metabolism)

1. Urine for reducing substances, glucose, ketones, urine pH (with pH meter rather than litmus paper).
2. Assess acid base status, anion gap $(Na^+K) - (HCO_3^+ Cl)$, normal 18-20 mmol/liter, glucose, Ca/Mg, liver enzymes, urea, creatinine, complete blood count, platelets, ammonia and lactate levels.
3. Common laboratory tests (sampling to be done early when child is sick).
    - Urine for chemical tests (DNPH, $FeCl_3$ test, etc)
    - Urine for aminoaciduria (paper chromatography)
    - Blood for amino acid quantification (column chromatography).
    - For galactosemia (galactose 1phosphate uridyl transferase enzyme estimation, galactose1 phosphate estimation in red blood cells).
    - Leucocyte enzyme assays (usually not helpful for acute metabolic disorders).
4. Specialized tests
    - High-pressure liquid chromatography (HPLC) of urine to quantitate amino acids.
    - Gas chromatography and mass tandem spectroscopy. Samples of blood and urine can be collected on a special filter paper. Blood can also be collected in heparin or EDTA tube and then put on the filter paper.
    - Enzyme essays in liver tissue, fibroblast cultures from skin, amniotic cells, and chorionic villous cells.

LABORATORY INVESTIGATIONS

Proper collection of specimens, laboratory experience in processing them, methodology of investigative procedure and interpretation of results are all important in arriving at a correct diagnosis. Sample of urine or blood should be taken when the patient is unwell, preferably at an early stage when the patient is still taking food orally, as certain disorders of organic acids or amino acids or galactose metabolism can be missed if patient has been on intravenous fluid for some time. Aminoaciduria and organic acidemia can be assessed by paper chromatography, column chromatography, gas chromatography and tandem mass spectrometry. The clinician and the laboratory staff should appreciate the scope and limitations of each method (Table 62.2). Paper chromatography can identify gross aminoaciduria whereas column chromatography measures actual level of amino acids. Gas chromatography is good for diagnosing elevated levels of organic acids or precursors. Tandem mass spectrometry is able to give precise analysis of most volatile and non-volatile organic acids and amino acids.[4] Hyperammonemia is a common finding in any sick child especially if the child has liver disease. Even in organic acidemia high level of ammonia is present because organic acids inhibit urea cycle enzymes, such as carbamyl phosphatase synthetase, resulting in increase levels of ammonia. Primary urea cycle disorders are not uncommon and require quantitative amino acid analysis for diagnosis. Along with high ammonia levels there may be increase in specific amino acids in plasma depending upon enzymatic block, while marked elevation of alanine and glutamine is seen in urea cycle disorders. Marked increase in orotic acid is present in OTC deficiency. In these disorders, enzyme levels can be measured in leukocytes (blood), liver and fibroblast (skin biopsy) cultures. These enzymes have to be measured in the organ where they are normally present. Antenatal diagnosis is possible in majority of cases with the help of DNA studies on (amniotic cells obtained by amniocentesis at 15-16 weeks gestation) chronic villous cells collected by chorionic villous sampling at 11-12 weeks or metabolite studies. Some countries do routine screening of all the newborn babies by paper chromatography, or assay of metabolites, or by tandem mass spectroscopy.

TREATMENT

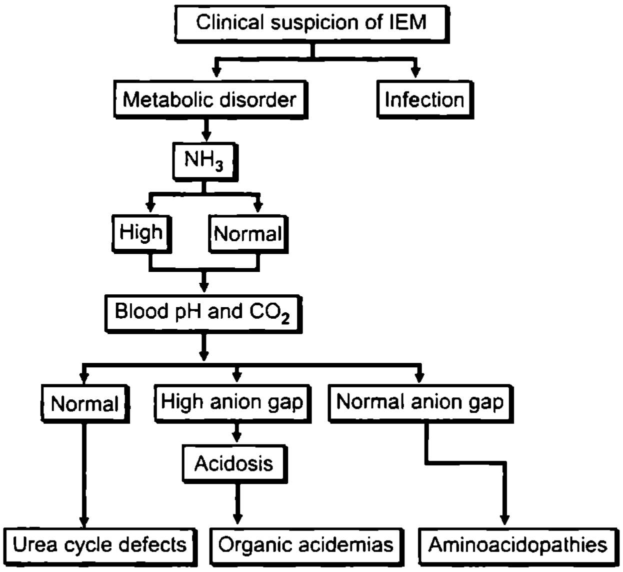
1. *Stop intake of proteins:* In the form of milk or other foods so as to limit the source of offending metabolite.
2. *Administer adequate calories:* In the form of oral glucose, glucose polymer solution or intravenous glucose (10-15%). Administering 60-70 Kcal/kg will help to stop breakdown of proteins in the body and hence decrease the offending amino acid metabolite. Insulin dextrose solution (one unit of insulin per 3-5 gm glucose) can create a temporary anabolic effect in several disorders, but should be avoided in urea cycle disorders.
3. *Supportive treatment:* In the form of correction of acid base imbalance, electrolyte disturbance and ventilatory support are needed. Exchange transfusion can also help temporarily, but is not good for urea cycle disorders, where peritoneal dialysis is preferred.
4. *Dialysis:* Majority of organic acid disorders have severe acidosis requiring large amounts of sodium bicarbonate which can result in hypernatremia. Bicarbonate in the peritoneal dialysate promptly corrects the acidosis, although organic acid precursors and ammonia come out slowly through peritoneal dialysis. In today's senario peritoneal dialysis as an modality to decrease ammonia levels is considered to be sub-optimal therapy. Continuous hemodialysis (CHD) or continuous hemodiafilteration via arteriovenous or venovenous route (CAVHDF/ CVVHDF) help to decrease the serum ammonia levels more rapidly and are the modalities of choice.[5,6] However, since the hemodialysis is not available in most places in India, peritoneal dialysis is still useful.
5. *Control of hyperammonemia:* Lowering ammonia levels (which may be due to UREA cycle disorder or secondary to organic acidemias and liver diseases, etc may be beneficial. The advantage of decreasing ammonia levels alone in cases with hyperammonemia except primary ammonia cycle disorders is debatable.[7] At levels of ammonia over 600 micromol/L chelating agents such as sodium benzoate or phenylacetate can be used. Sodium benzoate orally or intravenously is given as loading dose of 250 mg/kg followed by 250 mg/kg/day in divided doses. In India only the oral form of sodium benzoate is available. Hemodialysis, if available, would greatly help to decrease ammonia levels in 8 to 12 hours.
6. *Megavitamin cocktail:* Where facilities for proper diagnosis are not available and likelihood of inborn error of metabolism is strong, trial of megavitamin cocktail can be given.[8] These vitamins in large doses, acting as cofactors, may overcome the enzymatic blockage to some extent (Table 62.3). Carnitine is a carrier protein which helps fatty acids get into mitochondria and hence, is required for fatty acid metabolism. Secondary carnitine deficiency occurs in majority of the organic acidemias, and urea cycle disorders. Treatment with carnitine orally (50-100 mg/day) is of help.
7. *Dietary control:* Once the acute stage is over, offend-ing precursors have to be given in a controlled way in the diet so as to avoid recurrence of illness. Highly specialized diet, and milk formulae are available in the world market to control and treat various metabolic disorders, such as phenylketonuria, tyrosinemia, maple syrup urine disease, urea cycle disorders, organic acidurias, galactosemia, etc.

Table 62.3: Megavitamin cocktail

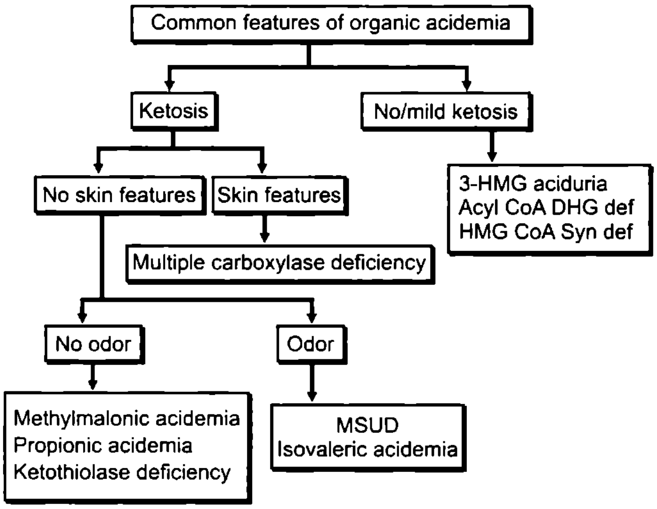
Assuming, final diagnosis is not possible due to lack of laboratory facilities and metabolic disease is strongly suspected ***Megavitamin Therapy*** can be given. There are no side effects and condition improves if the defect is mild and cofactor dependent.

- Thiamine 30 mg IM, in divided doses (maple syrup urine disease, pyruvate dehydrogenase deficiency)
- Riboflavin 30 mg IM, in divided doses (glutaric aciduria)
- Biotin 15 mg IM, in divided doses (propionic aciduria, multiple carboxylase deficiency)
- Vitamin B_{12} 1 mg IM, in divided doses (methylmalonic aciduria)
  Repeat daily if there is significant response till results of laboratory investigations are available.
- Secondary carnitine deficiency is common in cases of branched chain organic aciduria, and hyperlacticemia, etc. Carnitine orally 50-100 mg/day is helpful.

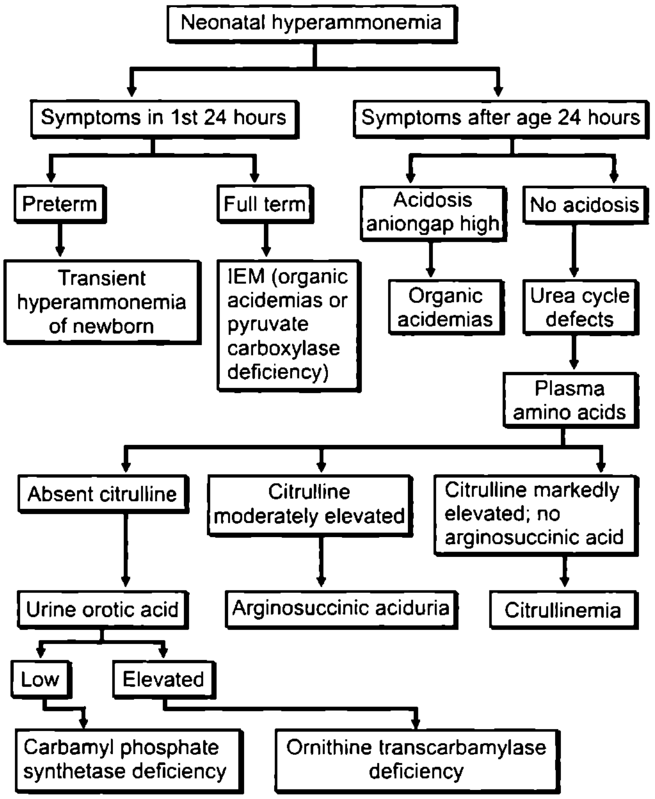
Flow chart 62.1: Initial approach to inborn error of metabolism


Clinical suspicion of IEM
Metabolic disorder
Infection
NH$_3$
High
Normal
Blood pH and CO$_2$
Normal
High anion gap
Normal anion gap
Acidosis
Urea cycle defects
Organic acidemias
Aminoacidopathies

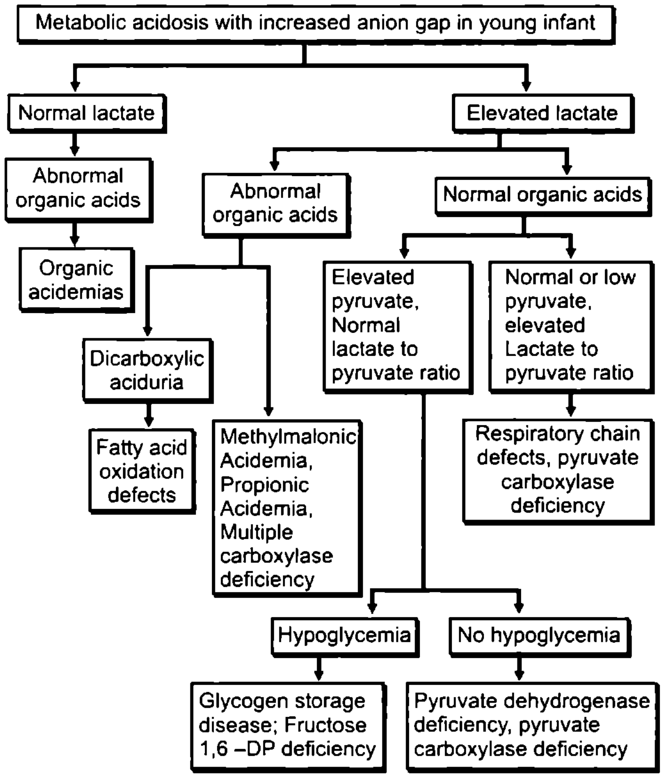
Flow chart 62.2: Organic acidemia


Common features of organic acidemia
Ketosis
No/mild ketosis
No skin features
Skin features
3-HMG aciduria
Acyl CoA DHG def
HMG CoA Syn def
Multiple carboxylase deficiency
No odor
Odor
Methylmalonic acidemia
Propionic acidemia
Ketothiolase deficiency
MSUD
Isovaleric acidemia

Flow chart 62.3: Neonatal hyperammonemia


Neonatal hyperammonemia
Symptoms in 1st 24 hours
Symptoms after age 24 hours
Preterm
Full term
Acidosis aniongap high
No acidosis
Transient hyperammonemia of newborn
IEM (organic acidemias or pyruvate carboxylase deficiency)
Organic acidemias
Urea cycle defects
Plasma amino acids
Absent citrulline
Citrulline moderately elevated
Citrulline markedly elevated; no arginosuccinic acid
Urine orotic acid
Arginosuccinic aciduria
Citrullinemia
Low
Elevated
Carbamyl phosphate synthetase deficiency
Ornithine transcarbamylase deficiency

Flow chart 62.4: Metabolic acidosis with increased anion gap


Metabolic acidosis with increased anion gap in young infant
Normal lactate
Elevated lactate
Abnormal organic acids
Abnormal organic acids
Normal organic acids
Organic acidemias
Elevated pyruvate, Normal lactate to pyruvate ratio
Normal or low pyruvate, elevated Lactate to pyruvate ratio
Dicarboxylic aciduria
Fatty acid oxidation defects
Methylmalonic Acidemia, Propionic Acidemia, Multiple carboxylase deficiency
Respiratory chain defects, pyruvate carboxylase deficiency
Hypoglycemia
No hypoglycemia
Glycogen storage disease; Fructose 1,6 –DP deficiency
Pyruvate dehydrogenase deficiency, pyruvate carboxylase deficiency

8. *Genetic counseling and prenatal diagnosis* In India majority of cases of IEM are diagnosed as septicemias, encephalopathy, hepatitis, etc and in some cases death occurs without proper diagnosis. As majority of disorders are inherited, it is important to establish the diagnosis of these disorders precisely so as to help the family with prenatal diagnosis in future pregnancies. Saving of blood and urine samples, and fibroblast culture (skin biopsy) in some cases, help to achieve this by further investigations. Once the diagnosis is confirmed, prenatal counseling can be offered in future pregnancies.[8]

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CHAPTER

63

Diabetic Ketoacidosis

Sukhmeet Singh, Praveen Khilnani

Diabetes mellitus is a syndrome of disturbed energy homeostasis caused by a deficiency of insulin or of its action resulting in abnormal metabolism of carbohydrate, protein, and fat. Diabetes mellitus is the most common endocrine-metabolic disorder of childhood and adolescence. Individuals affected by insulin-dependent diabetes confront serious burdens that include an absolute daily requirement for exogenous insulin, the need to monitor their own metabolic control, and the need to pay constant attention to dietary intake.

Morbidity and mortality stem from metabolic derangements and from long-term complications that affect small and large vessels and result in retinopathy, nephropathy, neuropathy, ischemic heart disease, and arterial obstruction with gangrene of the extremities.

CLASSIFICATION

Diabetes mellitus (DM) has been classified into two types: Type I and Type II.

Type I Diabetes (insulin-dependent diabetes mellitus, IDDM)

- It is characterized by severe insulinopenia and dependence on exogenous insulin to prevent ketosis and to preserve life. It occurs predominantly in childhood.
- It probably has some genetic predisposition and is likely autoimmune-mediated.

Type II Diabetes (non-insulin-dependent diabetes mellitus, NIDDM)

- Patients with type II diabetes are not insulin dependent and rarely develop ketosis.
- It generally occurs after age 40, and there is a high incidence of associated obesity. In patients with type II diabetes insulin secretion is generally adequate but insulin resistance is usually present. There is no associated genetic predisposition.
- Secondary diabetes can occur in response to other disease processes such as exocrine pancreatic disease (cystic fibrosis), Cushing syndrome, poison ingestion (rodenticides).

Type I Diabetes Mellitus

Prevalence of IDDM among school-age children in the US is 1.9 per 100 and the annual incidence in the US is about 12-15 new cases per 100,000.

Male to female ratio is usually equal. among African-Americans, the occurrence of IDDM is about 20-30 per cent of that seen in Caucasian-Americans. Peaks of presentation occur at 5-7 years of age and at adolescence.

Newly recognized cases appear with greater frequency in the autumn and winter. There is definite increased incidence of IDDM in children with congenital rubella syndrome.

Etiology and Pathogenesis of DM

Basic cause of clinical findings is sharply diminished secretion of insulin. The mechanisms that lead to failure of pancreatic b-cell function are likely autoimmune destruction of pancreatic islets.

IDDM is more prevalent in persons with Addison's disease, Hashimoto's thyroiditis, and pernicious anemia.

Eighty-ninty per cent of newly diagnosed patients with IDDM have anti-islet cell antibodiesProgressive destruction of b-cells leads to a progressive deficiency of insulin. As IDDM evolves, it becomes a permanent low-insulin catabolic state which feeding does not reverse. Secondary changes involving stress hormones accelerate the metabolic decompensation.

With progressive insulin deficiency, excessive glucose production and impairment of its utilization result in hyperglycemia with glucosuria when the renal threshold of ~ 180 mg/dL is exceeded.

The resultant osmotic diuresis produces polyuria, urinary losses of electrolytes, dehydration, and compensatory polydipsia.

Hyperosmolality as a result of progressive hyperglycemia contributes to cerebral obtundation in diabetic ketoacidosis (DKA).

Serum Osmolality= $\{\text{Serum Na}^+ + \text{K}^+\} \times 2 + glucose + BUN$

DEFINITION OF DIABETIC KETOACIDOSIS(DKA)

Patient with insulin deficiency leading to glucosuria, ketonuria, hyperglycemia, ketonemia, and metabolic acidosis. **In rare cases the Blood glucose is not elevated** (young or partially treated children as well as pregnant adolescents may present with near normal glucose values "euglycemic ketoacidosis"). So biochemical criteria include following:

1. Heavy glycosuria and ketonuria
2. Hyperglycemia (BG >11 mmol/l, >300mg/dL)
3. pH <7.3
4. Bicarbonate <15 mmol/l **and** 5 percent or more dehydration ± vomiting ± drowsy

Severity of Acidosis

Mild (venous pH: <7.30; bi-carbonate concentration: <15 mmol/L).

Moderate (pH<7.2; bicarbonate: <10). **Severe** (pH: <7.1; bicarbonate: <5).

Pathogenesis

DKA results from altered lipid metabolism due to insulin deficiency:

- increased concentrations of total lipids, cholesterol, triglycerides, and free fatty acids resulting in ketone body formation due to lack of insulin; the rate of formation exceeds the capacity for their peripheral utilization and renal excretion leading to accumulation of ketone bodies (acetoacetic acid, beta hydroxy butyric acid and acetone), and therefore, metabolic acidosis.
- With progressive dehydration, acidosis, hyperosmolality, and diminished cerebral oxygen utilization, consciousness becomes impaired, and the patient ultimately becomes comatose.

Clinical Manifestations of DKA

Classic presentation of diabetes in children is a history of polyuria, polydipsia, polyphagia, and weight loss, usually for upto one month. Twenty-five per cent of children present with dehydration, drowsiness as well as hyperventilation with diabetic ketoacidosis with no prior history of polyuria or polydipsia as the initial presentation leading to diagnosis of diabetes mellitus type I.

Laboratory Findings

Include glucosuria, ketonuria, hyperglycemia, ketonemia, and metabolic acidosis. Serum amylase may be elevated.

Leukocytosis is common

- Early manifestations of DKA are mild and include vomiting, polyuria and dehydration.
- More severe cases include Kussmaul respirations, odor of acetone on the breath.
- Abdominal pain or rigidity may be present and mimic acute appendicitis or pancreatitis.
- Exploratory laparotomy should be deferred unless intestinal perforation is suspected and diabetic ketoacidosis has been ruled out. Progressive dehydration and metabolic acidosis will cause further deterioration of neurological status.

Cerebral obtundation and coma ultimately ensue

- Diagnosis of IDDM is dependent on the demonstration of hyperglycemia in association with glucosuria with or without ketonuria.

DKA must be differentiated from acidosis and coma due to other causes

- Hypoglycemia, uremia, gastroenteritis with metabolic acidosis, lactic acidosis, salicylate intoxication and meningoencephalitis.

- DKA exists when there is hyperglycemia (> 300 mg/dL), ketonemia, acidosis, glucosuria and ketonuria.

PICU Management (Flow chart 63.1)

Management is essentially divided into 3 phases:
1. Treatment of ketoacidosis
2. Transition period
3. Continuing phase and guidance

Treatment of Ketoacidosis

Goals of treatment of DKA are intravascular volume expansion correction of deficits in fluids, electrolytes, acid-base status and initiation of insulin therapy to correct catabolism and further acidosis.

Intravascular volume expansion Hypovolemic shock is common, and must be recognized and aggressively treated. Dehydration is most commonly in the order of 10 to 15 per cent.

Initial fluid bolus should be isotonic saline (**0.9 percent saline or Ringer Lactate)** 20 ml/kg. This alone will often slightly lower the blood glucose.As much as 60 to 80 ml/kg fluid bolus may be required to stabilize hemodynamic status. Change the fluid type to **0.45 percent saline/5 percent dextrose or** add glucose to the fluid once the blood glucose has fallen to 150-200 mg/dl.

Volume of fluid: Once circulating blood volume has been restored, calculate fluid requirements as:-

Requirement = Maintenance + Deficit

Deficit (L) = % dehydration × weight (kg)

"Pseudohyponatremia" is often present.One should expect that the sodium (Na) level will rise during treatment.

Corrected Na = Measured Na + {(glucose – 100) × 0.016}.

If Na does not rise, true hyponatremia may be present (possibly increasing cerebral edema risk) and should be treated.

Bicarbonate (HCO_3) is almost never administered

Even severe acidosis is reversible by fluid and insulin replacement. Administration of insulin stops further ketoacid synthesis and allows excess ketoacids to be metabolized. Also, treatment of hypovolemia will improve decreased tissue perfusion and renal function, thus increasing the excretion of organic acids and reversing any lactic acidosis, which may account for 25 percent of the acidemia.

There are potential arguments against the use of bicarbonate. Of concern is that bicarbonate therapy may cause paradoxical CNS acidosis and that rapid correction of acidosis caused by bicarbonate will result in hypokalemia and may accentuate sodium load and contribute to serum hypertonicity. Bicarbonate administration leads to increased cerebral acidosis.

HCO_3^- combines with H^+ and dissociated to CO_2 and H_2O. Whereas bicarbonate passes the blood-brain barrier slowly, CO_2 diffuses freely, thereby exacer-bating cerebral acidosis and cerebral depression. Indications for bicarbonate administration include severe acidosis (pH < 6.9) leading to cardiorespiratory compromise. In addition, alkali therapy may increase hepatic ketone production, thus slowing the rate of recovery from the ketosis.

Fluid and insulin replacement without bicarbonate corrects ketoacidosis.

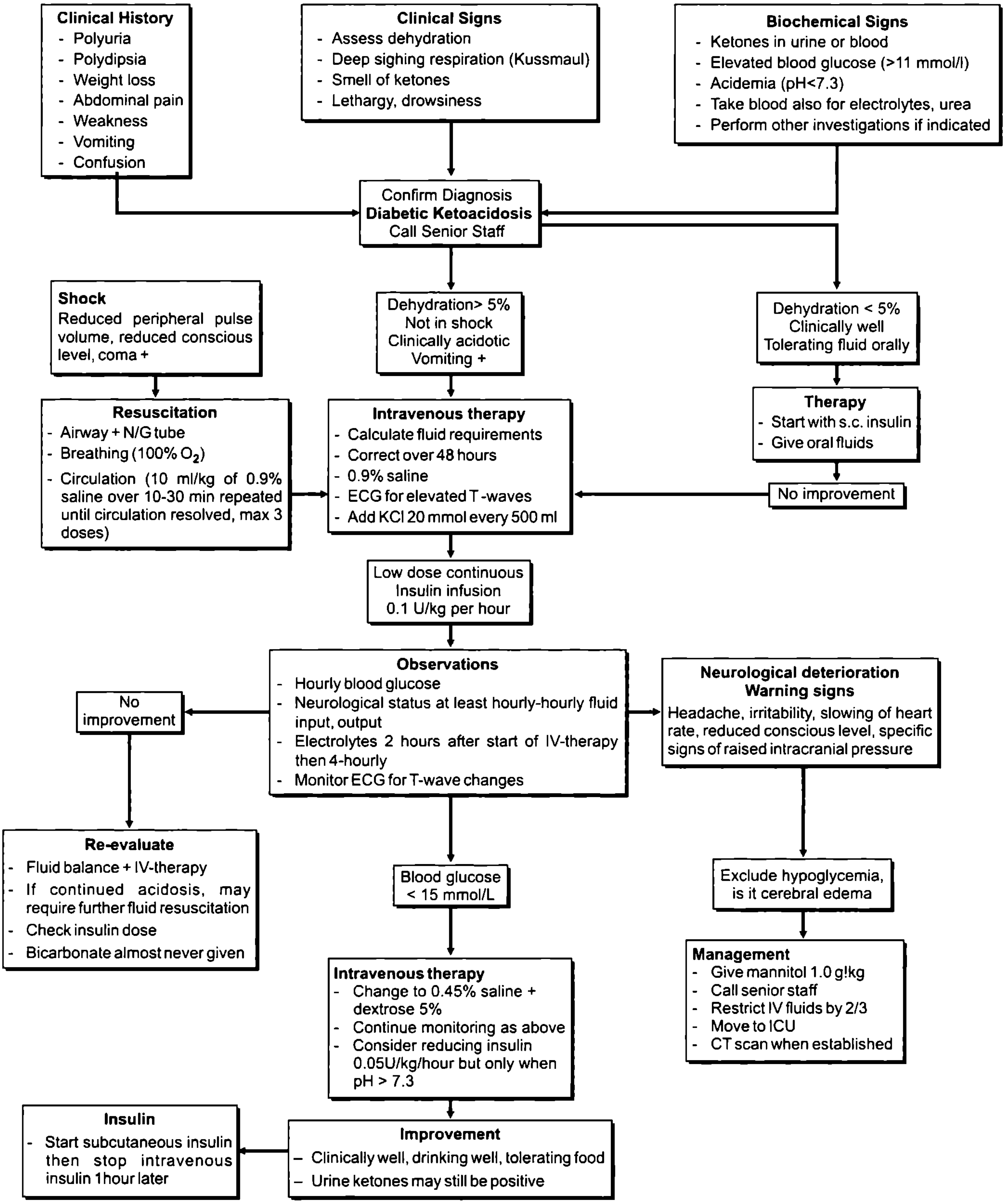
Potassium

Serum potassium (K^+) is often elevated due to acidosis causing movement of potassium ion out of the cell into intravascular space, though total body K^+ is depleted.

K^+ therapy is started early as resolution of acidosis and the administration of insulin will cause a further decrease in serum K^+ concentration. Administration of insulin and the correction of acidosis will drive potassium back into the cells, decreasing serum levels. Start potassium replacement immediately if the patient is hypokalemic; otherwise, start potassium concurrent with starting insulin therapy. If the patient is hyperkalemic, defer potassium until urine output is documented. If serum potassium is not available before completion of resuscitation, ECG monitoring is done before potassium is added to the infusion.

- Start potassium replacement as soon as resuscitation is completed and the ECG doesn't show elevated T-waves (or if potassium is not elevated).
- **Potassium chloride 40 mmol is usually added to each liter** of saline infusion. (Add 20 mmol KCl to every 500 ml bag of fluid).

Flow chart 63.1: Management of diabetic ketoacidosis
(Courtesy: Dr Sukhmeet Singh, Ludhiana)


Clinical History
- Polyuria
- Polydipsia
- Weight loss
- Abdominal pain
- Weakness
- Vomiting
- Confusion
Clinical Signs
- Assess dehydration
- Deep sighing respiration (Kussmaul)
- Smell of ketones
- Lethargy, drowsiness
Biochemical Signs
- Ketones in urine or blood
- Elevated blood glucose (>11 mmol/l)
- Acidemia (pH<7.3)
- Take blood also for electrolytes, urea
- Perform other investigations if indicated
Confirm Diagnosis
Diabetic Ketoacidosis
Call Senior Staff
Shock
Reduced peripheral pulse volume, reduced conscious level, coma +
Dehydration> 5%
Not in shock
Clinically acidotic
Vomiting +
Dehydration < 5%
Clinically well
Tolerating fluid orally
Resuscitation
- Airway + N/G tube
- Breathing (100% O2)
- Circulation (10 ml/kg of 0.9% saline over 10-30 min repeated until circulation resolved, max 3 doses)
Intravenous therapy
- Calculate fluid requirements
- Correct over 48 hours
- 0.9% saline
- ECG for elevated T-waves
- Add KCl 20 mmol every 500 ml
Therapy
- Start with s.c. insulin
- Give oral fluids
No improvement
Low dose continuous
Insulin infusion
0.1 U/kg per hour
Observations
- Hourly blood glucose
- Neurological status at least hourly-hourly fluid input, output
- Electrolytes 2 hours after start of IV-therapy then 4-hourly
- Monitor ECG for T-wave changes
No improvement
Neurological deterioration
Warning signs
Headache, irritability, slowing of heart rate, reduced conscious level, specific signs of raised intracranial pressure
Re-evaluate
- Fluid balance + IV-therapy
- If continued acidosis, may require further fluid resuscitation
- Check insulin dose
- Bicarbonate almost never given
Blood glucose
< 15 mmol/L
Exclude hypoglycemia,
is it cerebral edema
Intravenous therapy
- Change to 0.45% saline + dextrose 5%
- Continue monitoring as above
- Consider reducing insulin 0.05U/kg/hour but only when pH > 7.3
Management
- Give mannitol 1.0 g!kg
- Call senior staff
- Restrict IV fluids by 2/3
- Move to ICU
- CT scan when established
Insulin
- Start subcutaneous insulin then stop intravenous insulin 1hour later
Improvement
– Clinically well, drinking well, tolerating food
– Urine ketones may still be positive

Phosphate

Depletion of intracellular phosphate occurs and phosphate is lost as a result of osmotic diuresis. Phosphate depletion persists for several days after resolution of DKA. However, prospective studies have failed to show significant clinical benefit from phosphate replacement.

- There is no evidence that replacement has clinical benefit. Severe hypophosphatemia should be treated.
- Potassium phosphate salts may be used as an alternative to or combined with KCl.
- Administration of phosphate may induce hypocalcaemia.

Insulin therapy Continuous infusion of low-dose insulin IV (~ 0.1 U/kg/hr) is effective, simple and physiologically sound.

- Goal is to slowly decrease serum glucose (< 100 mg/dL/hr).
- Frequent laboratory (hourly blood sugar) and blood gas analyses (four to six hourly for first 24 hours) are obtained to ensure ongoing resolution of metabolic acidosis.
- "Maintenance" IV fluid at a rate of 2000-2400 cc/m^2/day consists of quarter NS and 5 per cent Dextrose is added to IVF when blood glucose is < 250 mg/dL (alternatively standard pediatric maintenance fluid calculation can be used; 40 cc/hr in a 10 kg child, 60 cc/hr in 20 kg child). 20 meq/l potassium chloride and 20 mEq/l potassium phosphate may be added to maintenance fluid.
- Insulin is used to treat acidosis, not hyperglycemia. If blood sugar is below 150 mg/dl, insulin drip can be temporarily stopped for one hour untill blood sugar rises above 200 mg/dl.
- Physiological purpose of insulin therapy is to increase glucose entry into the cell, to prevent ongoing production of ketone bodies.

With this regimen, acidosis is usually fully corrected in 24 to 48 hours.

Do not stop insulin infusion or decrease below 0.05 units/kg per hour because a continuous supply of both insulin and glucose substrate is needed to promote anabolism and reduce ketosis.

- **If the biochemical parameters of ketoacidosis (pH and anion gap) do not improve**, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin (e.g., infection, errors in insulin preparation, or adhesion of insulin to tubing with very dilute solutions).

There is evidence that **IV bolus of insulin** is not necessary. However, a bolus may be used at the start of insulin therapy, if insulin treatment has been delayed.

In unusual circumstances in which IV route is not possible, the **IM or SC route of insulin administration** has been used effectively. However, poor perfusion will impair the absorption of insulin.

Cerebral Edema

Cerebral edema typically occurs 4 to 12 hours after treatment is activated but can be present before treatment has begun or may develop any time during treatment for DKA.

The signs and symptoms of cerebral edema include:

- Headache and slowing of heart rate
- Change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
- Specific neurological signs (e.g. cranial nerve palsies)
- Rising BP, decreased O_2 saturation
- Abnormal posturing

More dramatic changes such as convulsions, papilloedema, and respiratory arrest are late signs associated with extremely poor prognosis.

Once the child is stable, exclude other D/D by CT scan-other intracerebral events may occur (thrombosis, hemorrhage, and infarction)

Cerebral edema is the major life-threatening complication seen in the treatment of children with DKA, usually developing several hours after the institution of therapy.Therapy of cerebral edema includes treatment with mannitol and controlled elective ventilation. Excessive use of fluids, use of bicarbonate, and large doses of insulin have been linked to the increased formation of cerebral edema.While **Intubation and ventilation** may be necessary. However, aggressive hyperventilation has been associated with poor outcome in DKA-related cerebral edema.

Fluids are limited to approximately 3 L/m^2/24 hours. The cause of cerebral edema during treatment remains unclear. However, too rapid reduction in intravascular osmolality may aggravate the process. It seems prudent therefore that rehydration should occur more slowly in children with DKA than in other causes of dehydration.

Once mental status, dehydration, electrolytes and acidosis corrected (usually 24 hr).

Meal may be given. If no vomiting occurs, subcutaneous insulin therapy can be safely begun.

Subcutaneous insulin therapy and further education should then be initiated.

- Total dose of insulin is given is 1 unit/kg/day.
- Insulin drip discontinued 1hr after sq insulin dose.
- Two-third dose may be given in am, one-third dose in pm. Am dose can be divided as one-third regular insulin and two-third intermediate/long acting.
- Long-term management and patient education are beyond the scope of this discussion.

As a word of caution hypoglycemic reactions (Insulin Shock) should be suspected and aggressively treated. Clinical symptoms and signs include pallor, sweating, apprehension, trembling, tachycardia, hunger, drowsiness, mental confusion, seizures and coma management includes administration (if conscious) of carbohydrate-containing snack or drink.

Glucagon 0.5 mg is administered to an unconscious or vomiting child. Remember, while hyperglycemia may be tolerated and treated slowly, but since hypoglycemia can kill, one must be vigilent regarding prompt detection and treatment.

SUMMARY

Diabetic ketoacidosis should be suspected in all dehydrated children.Early diagnosis is the key to survival.

Following steps are important in management:

- Admission to pediatric intensive care unit, early hemodynamic stabilization with isotonic fluids, correction of hypokalemia and correction of acid base status by early insulin therapy and prompt treatment of associated hypoglycemia.
- Bicarbonate therapy should be avoided, and should neurological deterioration and cerebral edema occur, immediate measures for reducing the intracranial pressure such as mechanical ventilation and mannitol should be initiated.

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CHAPTER

Acute Renal Failure in Pediatric Intensive Care Unit

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With increasing survival and expectations, with high level of delivery of intensive care to very sick children it is rapidly becoming common to see children with acute renal failure (ARF) in intensive care units. In a critically ill child renal dysfunction is common. Causes of renal insufficiency are multi-factorial, kidney is an innocent bystander. In most cases it is affected secondarily by a primary disease process. In an intensive care of a tertiary referral hospital offering multiple subspecialities and looking after critical ill children, primary nephrological problems are relatively uncommon causes of ARF. The patients with ARF in intensive care unit usually have multiple organ dysfunction, often requiring respiratory or circulatory support, hence are admitted to intensive care units.As the technology has advanced, the level of sophistication has increased and the complexity of disease process requires a concept of tertiary health care. Team approach and establishment of well recognized units offering a team of doctors is needed to look after the critically ill children. This is a must for managing a child with ARF for favorable outcome.

Definition

ARF is defined as an abrupt decrease in renal functions, mainly regulation of water, electrolytes, acid base balance and removal of nitrogenous waste products. The hallmark of ARF is oliguria though normal urine output or polyuria can occasionally be associated with ARF. In the pediatric ICU setting the definition of ARF must be broadened to include those patients who need large volumes of fluids and blood products and their kidneys are unable to increase the urine output sufficiently to avoid fluid overload. In these patients, serum creatinine and blood urea levels may not rise, and the urine output may exceed 1 ml/kg/hr. Oliguria is defined as reduction in urine output less than 300 ml/sq meter BSA (body surface area)/day, or in a neonate less than 0.6 ml/kg body wt/hour.[1] ARF usually occurs in patients with previously normal kidneys but occasionally it may be superimposed on a pre-existing renal disease which gets further worse in an unfavorable environment. The incidence of ARF varies depending on the type of cases the institution is looking after. It is about 1-2 percent of all pediatric admissions and 10-15 percent of all pediatric intensive care admissions in a tertiary referral hospital.[2]

Physiology

Urine is produced by glomerular filtration, which depends on the maintenance of a relatively high perfusion pressure within the glomerular capillary and an adequate renal blood flow. The glomerular blood flow is auto-regulated by pre-glomerular arteriole untill mean arterial pressure falls at around 60 mmHg. Arteriolar dilatation (mediated by prostaglandins and partly by myogenic factors) occurs as blood pressure falls, the reverse happens when blood pressure rises. The blood flow is further maintained by constriction of post-glomerular arterioles if mean arterial pressure falls further and perfusion pressure is not maintained, this is mediated by Angiotension II.

The proximal tubules reabsorb most of the filtered solute to keep Na, electrolytes and fluid balance. The distal tubule regulates elimintation of potasium, water and non-volatile hydrogen ions. In a hypotensive or hypovolemic state maximum amount of glomerular filtrate is absorbed by proximal tubules so that very little reaches to distal tubules.

The energy required for tubular functions comes from aerobic metabolism within the mitochondria of tubular cells. The oxidative metabolism is sensitive to the effects of ischemia and hypoxia. The cells of the thick ascending limb of the loop of Henle are metabolically very active hence are most vulnerable to ischemia/hypoxia.

Causes of ARF

Traditionally and historically causes of ARF have been categorized into *Pre-renal, Intrinsic renal* and *Post-renal* groups. As mentioned earlier, cause of ARF is multifactorial and in a modern pediatric intensive care unit, primary renal causes of ARF are uncommon. In a tertiary center looking after sick children, septicemia, multiorgan failure, shock, hypoxia, congenital heart disease, post-operative cardiac surgeries, fulminant hepatitis, malignant diseases needing chemotherapy, organ transplants are the most common causes of ARF.

Overall in India diarrheal dehydration is still the commonest cause of ARF. Usually these cases are managed with fluid replacement and are not admitted in the intensive care unit. With increasing use of various drugs, it is common to see drug related ARF. Drugs may cause nephrotoxicity, tubular damage or interstitial nephritis. In majority of cases drugs either precipitate or worsen renal failure (Table 64.1). Epidemics of ARF have occurred due to diethylene glycolcontaminated glycerin used to manufacture acetaminophen.[3] Non-steriodal antiinflammatory drugs can produce an allergic interstitial nephritis and in a sick patient, they impair compensatory mechanisms that maintain glomerular perfusion and medullary blood flow to ascending limb of the loop of Henle. A single dose may be sufficient to precipitate failure of a stressed kidney.

Clinical Features

There are no specific symptoms of ARF and infact in early stages apart from oliganuria child may not show any symptoms. Once the glomerular filtration rate (GFR) falls to less than 10-15 percent of the normal, non-specific symptoms such as tiredness, poor appetite, nausea, vomiting may appear. Oligoanuria, raised blood urea and creatinine are the early indications of ARF. In advance stage altered sensorium, convulsions due to dyselectro-lytemia, uremia or hypertensive encephalopathy may occur. The breathing may be rapid and deep due to metabolic acidosis or pulmonary edema. There may be symptoms suggestive of fluid overload interms of swelling, edema. However, features of an underlying cause of ARF usually supersedes symptoms of ARF.

Table 64.1: Drugs causing ARF

1. *Acute Tubular Injury:*
   - Ibuprofen, Ketorolac, Acyclovir, ACE (angiotensin converting enzyme) Inhibitors, Cyclosporin A, intravenous globulins, radiocontrast dyes for angiography/pyelography.
2. *Direct Cellular Toxins:*
   - *Antibiotics:* Aminoglycosides, Cephalosporins, Sulphonamides, Amphotericin B
   - *Chemotherapy agents:* Cisplatin, doxorubicin, methotrexate.
   - *Others:* furosemide. NSAIDs (non-steroidal anti inflammatory agents), heavy metals, Betablockers.
3. *Acute Tubulo Interstitial nephritis:*
   - *Antibiotics:* Ampicillin, cephalosporins, sulphonamides, Co-trimoxazole, quinolones, Betalactams, Vancomycin.
   - *Others:* Cimetidine, NSAIDs, Captopril, furosemide, Thiazides, Phenytoin, Rifampicin, Allopurinol.

Diagnostic Approach

Detailed history and good clinical examination still remain the most important tools for evaluating any serious clinical disorder and ARF is not exception. History of suggestive fluid loss, blood loss during a procedure or surgery, hypoxia may alert the high possibility of impending ARF. Sudden passage of dark red urine and jaundice along with blood transfusion or drugs may indicate acute intravascular hemolysis or Glu-6 Phosphate dehydrogenase deficiency. Abdominal colic, hematuria, and dysuria may suggest renal calculi with or without urinary infection. Complete anuria may occur in urinary obstruction. History of dysentry, pallor and petechiae with oligoanuria suggest Hemolytic uremic syndrome (HUS). In neonates history of perinatal hypoxia, oligohydramnios may give indications for impending ARF.

Clinical Examination

It may give clues towards the cause of ARF. Monitoring of blood pressure with appropriate sized cuff is of paramount importance. It is not uncommon to record wrong blood pressure readings if appropriate precautions are not taken. Use of various drugs causing nephrotoxicity and hence ARF should be kept in mind while treating a sick child. Multisystem involvement with prolonged fever indicates collagen disorder or vasculitis. ARF may occasionally be superimposed on chronic renal disease. Features such as failure to thrive and growth retardation, hypocalcemia, hyperphosphatemia, renal osteodystrophy, small contracted kidneys, indicate chronicity which may have not been diagnosed earlier. It is essential that all children undergoing cardiac surgery especially with congenital heart disease have their renal (anatomical and functional) status evaluated prior to cardiac surgery. Assessment of fluid intake, urine output and other losses over period of illness shall help to assess fluid balance. Overzealous restriction of fluids in established case of ARF often leads to hypoglycemia particularly in neonates and small children. Measurement of skin temperature (toe temperature) and core temperature (rectal temperature) may help to assess degree of systemic vasoconstriction. Cold extremities with poor peripheral perfusion indicated by delayed capillary filling in nails are suggestive of poor tissue perfusion, vasoconstriction and impending shock. Various indices have been described to differentiate pre-renal ARF from established ARF (Table 64.2). However, in clinical practice its usefulness is of doubt mainly because of the fact that ARF is usually multifactorial i.e. both pre-renal and renal factors may contribute towards the illness and also majority of these children receive diuretics which makes these indices useless to differentiate pre-renal and renal ARF. To assess the pre-renal element of ARF, fluid challenge with 20-30 ml/kg of Isotonic solution over 45-60 minutes followed by furosemide 2 mg/kg intravenously results in good urine output (2-3 ml/kg over 2-3 hours).

Table 64.2: Indices used to differentiate Pre-renal ARF from established ARF (Indices for neonates are in parentheses)

Established renal	Pre-renal
Urinary Sodium (mEq/L) > 40 (> 60)	< 20 (< 30)
Urinary Osmolality (m Osm/kg)	> 500 (> 400)
	> 300 (< 350)
Urine/Plasma creatinine < 20	> 40
FENa% > 1 (> 3)	< 1 (< 3)

$$\text{FENa (\%)} = \frac{\text{Urine Na} \times \text{Serum Creatinine}}{\text{Serum Na} \times \text{Urine Creatinine}} \times 100$$

FENa (Fractional excretion of sodium)

Investigations

Appropriate battery of investigations to establish the diagnosis of ARF and its causes is necessary. The investigations are usually guided by clinical history, examination and possible cause of ARF. Investigations to judge life threatening consequences of renal dysfunctions such as hyperkalemia, acidosis, anemia, etc. are sent as an emergency.

1. Simple investigations are extremely helpful for the diagnosis and management of managing ARF. Urine examination for red cells, casts, presence of eosinophils, pyuria, bactiurea, morphology of red cells by phase contrast microscopy give lot of clues towards the diagnosis. Peripheral smear of blood to indicate type of anemia, morphology of RBCS, toxic granules, and platelet count are helpful.
2. Routine workup along with organ specific investigations if needed such as hepatitis profile, and echocardiogram may be required. For renal causes immune profile (CH50, C3, C4 ANA, Anti DNA antibodies, ANCA, ASO Tites, Anti DNA'S B) may be done.
3. Ultrasound of kidneys and bladder remains most helpful investigation in ARF. In experienced hands it gives very useful information. If possible Doppler scan should be done to assess renal blood flow and any evidence of thrombosis in renal blood vessels. It easily excludes obstructive causes of ARF.
4. Renal Biopsy is usually not required in most cases. Early renal biopsy is indicated if diagnosis such as rapidly progressive nephritis, vasculitis, systemic renal diseases is suspected as intensive immuno suppressive therapy may be required in early stage of ARF. If ARF persists for over 2-3 weeks renal biopsy is indicated from prognostic

point of view to assess cortical necrosis or tubular necrosis.

5. Radio Isotope Scans such as DMSA, DTPA scans are required rarely to diagnose cortical scarring, necrosis, vasculitis, obstruction. Angiography remains the gold standard test to diagnose thrombosis, and is also helpful along with other tests to diagnose renal artery stenosis and vasculitis.

Management

Supportive Management

In initial stages if oligoanuria persists bladder catheterization, central venous pressure monitoring (CVP) are required to determine the adequacy of fluid replacement and guide further management. Circulation must be corrected before any specific intervention is started. Mean systemic blood pressure should be maintained over 50th percentile for age with the help of fluids, colloids, without causing fluid overload, bloodsugar over 100 mg/dl in older children and 50 mg/dl in neonates to avoid hypoglycemia. Inotropic drugs are helpful to maintain the blood pressure and hence renal perfusion. Systemic hypertension over 95th percentile for age should be treated. In case of severe hypertension, blood pressure should be brought down gradually over 48-72 hours so as to maintain tissue perfusion. Other supportive treatment to maintain temperature, good nursing care, strict input-output charting, adequate oxygenation are all essential part of over all treatment.

Specific Treatment

Role of Diuretics

Diuretics may improve urine output but not the glomerular filtration rate i.e. the renal function. Urine produced after diuretics treatment is of poor quality, hence is of no importance. Renal recovery, need for dialysis and death are not different in patients who received diuretics as compared to control.[4] Infact there is further danger of side effects due to diuretics such as ototoxicity, interstitial nephritis and hypotension. Diuretics may be indicated and are of help if good urine output is produced in cases of pulmonary edema. High urine output also helps to prevent intratubular precipitation with intravascular hemolysis, hyperuricemia and myoglobinurea.

Dopamine

Low dose dopamine or so called nephrological (renal) doses of dopamine causing renal vascular dilatation, natriuresis and diuresis has been recommended for years. There was always some doubts about its usefulness and recent studies indicate that routine use of dopamine is not recommended as studie have failed to show any beneficial effect.[5] However, dopamine and other inotropic drugs are useful for maintaining mean arterial pressure and hence renal perfusion. In some cases within 24 hours of use it produces diuresis which may be of some help. It is advisable to use dopamine through central line due to risk of ischemic skin necrosis caused by extravasation and direct vasoconstrictive effect.

Others

Several experimental drugs such as thyroxin, calcium channel blockers antioxidants, peptide growth factors, insulin like growth factor-1, nitric oxide synthetase inhibitors have been shown to be beneficial in animal studies. Results of clinical trials have not indicated any significant benefits. Thus there is no specific drug therapy to treat ARF and the treatment is supportive in nature.

Surgical Role

Any obstruction causing ARF or precipitating it, should be diagnosed early and be dealt with urgently. Obstruction of upper collecting system can be relieved by percutaneous nephrostomy under ultrasonography usually at the bedside. Lower tract obstruction is relieved by ureterostomy, suprapubic or urethral catheterization. Definitive surgery is done once patient's condition is stable.

Renal Replacement Therapy

Functions of kidney are briefly listed in Table 64.3. If in a sick patient kidneys fail to function and situation arises when it may be detrimental to patient life, renal replacement therapy (RRT) has to be instituted. RRT should be started in anticipation rather than to wait for absolute indications as

Table 64.3: Functions of kidneys

Role of maintaining the internal environment:
- Elimination of water soluble waste products of metabolism except carbon dioxide such as urea, creatinine.
- Control of fluid, electrolyte, Acid-base homeostasis.
- Elimination of water soluble drugs.
- Endocrine functions (Erythropoietin, VIT D-Parathyroid Hormone Axis and Renin)

customarily mentioned in standard textbooks.[6] Also each patient has to be individualized for need of dialysis, e.g. Serum potasium over 5.5 mmol/L may be dangerous for a post-cardiac surgery patient as compared to a neonate with serum potassium of 7 mmol/L, which is better tolerated. A child with multiorgan failure needs dialysis early as compared to patient with ARF secondary to nephrotoxin. In a similar way severe intrabdominal sepsis such as fecal peritonitis with ARF needs early intervention as blood urea concentrations rise rapidly. Conservative treatment in ARF includes fluid balance (Insensible loss + loss via urine, nasogastirc and others vs oral intake, intravenous fluid, blood/blood products, and volume of drugs), control of sodium, restriction of potassium (rarely extra supplements to be given in obstructive uropathy) and treatment of hyperkalemia, control of blood pressure, treatment of anemia with small frequent blood transfusion (rarely erythropoietin is used in ARF, if anemia prolongs over days to weeks). Calcium and phosphorous homeostasis is usually not a serious problem in ARF. Acidemia may need bicarbonate supplements.

If above measures fail, removal of waste products and extra fluid is achieved by dialysis. By dialysis, space is also created so that in oligoanuric patients oral or intravenous fluids can be given to maintain nutrition and blood sugar. Blood or blood products and various medications can be given without the fear of fluid overload or pulmonary edema. Dialysis removes waste products such as urea, creatinine so a state of well-being is created. Hyperkalemia which can be life threatening is readily controlled. Sodium balance is also achieved. Dialysis also helps to normalize blood pressure by removal of excess fluid. Acidosis is readily corrected.

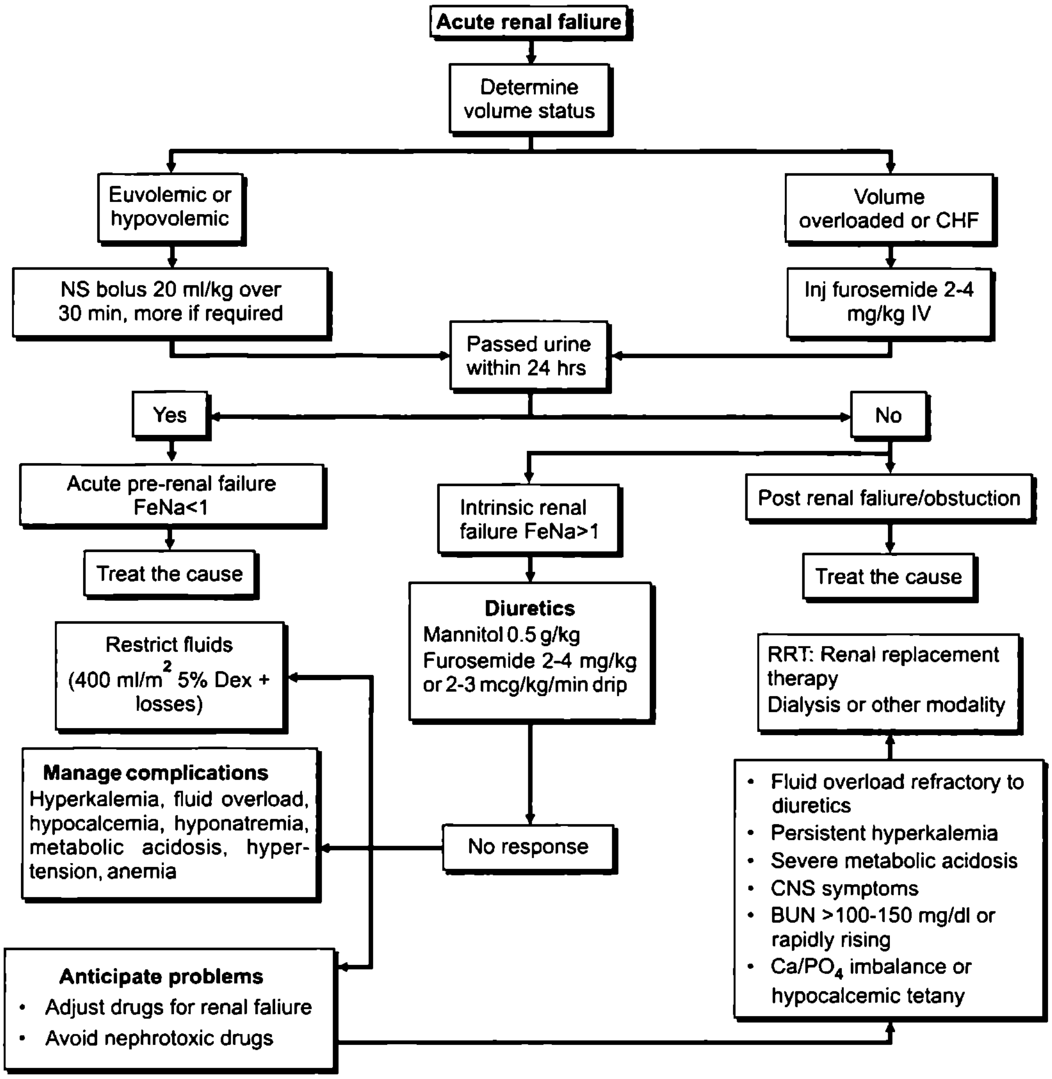
Modes of Dialysis

Various modes of dialysis are available. There is no evidence that outcome is better with any one particular technique in most of the cases. Available facilities and expertise of doctors, nurses, age and weight of the patient, hemodynamic status of the child, integrity of peritoneal membrane and abdominal cavity, availablity of vascular access, and cost are the consideration before deciding the mode of dialysis.

Peritoneal Dialysis (PD)

It is the most commonly used mode of treatment of ARF in childhood because of its simplicity, availability, relative safety and effectiveness. However, it can be unpredictable. Continuous hemofiltration (HF) with or without hemodialysis (HD) via arterio venous (AV) route or venovenous (VV) route (CAVHD/CAVHF/CVVHD/CVVHF) is becoming rapidly popular in well established renal units. It is now possible to do HF/HD even in a neonate. Although it is expensive, needs expertise of doctors and nurses, it is highly reliable and predictable. The outcome is perhaps better in those who have cerebral edema or pulmonary edema. The clinical situation associated with hyperammonemia also shows better response with continuous HD.[7] In our unit PD is the preferred choice for ARF, CVVHDF is reserved for those where peritoneal cavity cannot be used, problem arises after use of PD or if PD is not effective. Occasionally if ARF is prolonged over 2 weeks or so in older children HD is preferred, in smaller children with help of permanent Tenckoff's catheter continuos ambulatory peritoneal dialysis (CAPD) or with the help of a machine continuous cyclical peritoneal dialysis (CCPD) is used. This helps immobilizing patients and treatment can be continued outside intensive care if other medical problems are settled. Ideally each pediatric unit should be able to switch from one mode of dialysis to another as the situation demands and all modes of dialysis and expertise should be available. Renal failure or complications due to dialysis causing death should be an unacceptable cause of death in a tertiary referral hospital. The only exception being if a

Flow chart 64.1: Acute renal failure


Acute renal faliure
Determine volume status
Euvolemic or hypovolemic
Volume overloaded or CHF
NS bolus 20 ml/kg over 30 min, more if required
Inj furosemide 2-4 mg/kg IV
Passed urine within 24 hrs
Yes
No
Acute pre-renal failure FeNa<1
Intrinsic renal failure FeNa>1
Post renal faliure/obstuction
Treat the cause
Treat the cause
Diuretics
Mannitol 0.5 g/kg
Furosemide 2-4 mg/kg or 2-3 mcg/kg/min drip
Restrict fluids (400 ml/m2 5% Dex + losses)
RRT: Renal replacement therapy
Dialysis or other modality
Manage complications
Hyperkalemia, fluid overload, hypocalcemia, hyponatremia, metabolic acidosis, hypertension, anemia
No response
Fluid overload refractory to diuretics
Persistent hyperkalemia
Severe metabolic acidosis
CNS symptoms
BUN >100-150 mg/dl or rapidly rising
Ca/PO4 imbalance or hypocalcemic tetany
Anticipate problems
Adjust drugs for renal faliure
Avoid nephrotoxic drugs

CHF: Congestive heart failure *(Courtesy: Amit Gupta, MD)*

conscious decision has been made not to treat ARF in the face of another non-recoverable disease (Flow chart 64.1).

Outcome

Team approach in a sick child is of paramount importance. Treatment of primary cause of ARF is essential. These cases have to be managed in a intensive care where a team of dedicated doctors, nurses and paramedical staff is needed. Importance of nutrition can not be over emphasised particulary in our country where subclinical malnutrition is wide spread. Without providing adequate calories and looking after the nutrition all the hard work done can be easily lost.[8] Infection still remains the commonest cause of death in ARF. Infections should be avoided by meticulous handling of all the lines and good hand washing. Unnecessary use of prophylatic antibiotics should be discouraged. At the same time prompt diagnosis and appropriate treatment of infection is essential. The stress on the family should never be underestimated and psychosocial support, keeping the family regularly informed and discussing various problems shall always help to keep the family on doctor's side. With the help of dedicated team and technology mortality has been reduced considerably and overall it is 10-15 percent. Long-term sequelae are also uncommon and only 1-2 percent children later on have mild problems such as hypertension, tubular dysfunctions, etc.

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CHAPTER

Renal Replacement Therapy in the Pediatric Intensive Care Unit

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Renal replacement therapy (RRT) implies replacing the functions of the kidney in renal failure. Dialysis is one of the modalities of RRT. Majority of children with ARF (acute renal failure do not need dialysis. Conservative treatment as discussed in the chapter of ARF, usually is sufficient till the kidney recovers.

However, it is essential to remember that those cases who need dialysis, it should be done earlier rather than later. Here the discussion of RRT is only limited to acute renal failure (ARF) with particular with reference to dialysis. Also emphasis shall be on the practical aspects of dialysis in ARF. There are three main modalities of dialysis used in ARF in children:

1. Peritoneal Dialysis (PD)
2. Hemodialysis (HD)
3. Continuous venovenous hemofiltration or hemodiafiltration (CVVH/CVVHD)

PHYSIOLOGICAL PRINCIPLES OF DIALYSIS

Solute removal (urea, creatinine, K^+, etc) is termed as "Clearance" and fluid removal is called as "ultrafiltration". In a patient with ARF either of the two or both, clearance and ultrafiltration may be important. There are two transport mechanisms involved in dialysis: Diffusion and convection (Fig. 65.1). Diffusion is driven by solute concentrate gradient and convection transport occurs when solute is swept through the membrane by a moving stream

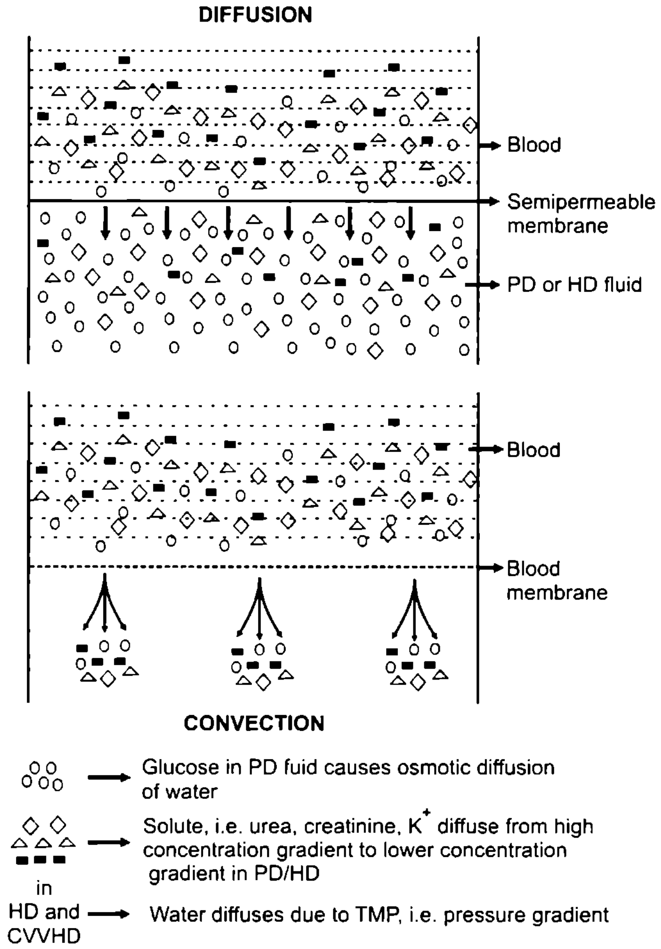
DIFFUSION
Blood
Semipermeable membrane
PD or HD fluid
Blood
Blood membrane
CONVECTION
Glucose in PD fuid causes osmotic diffusion of water
Solute, i.e. urea, creatinine, K+ diffuse from high concentration gradient to lower concentration gradient in PD/HD
in HD and CVVHD
Water diffuses due to TMP, i.e. pressure gradient

Fig. 65.1: Diffusion and convection involved in dialysis

of ultrafiltrate. Both mechanisms are responsible for dialysis in PD, HD and CVVHD. In CVVH dialysis occurs via convection only.

SELECTION OF MODALITY

Each modality has its advantages and disadvantages. The selection of modality will depend on the experience and expertise of an individual center and patient's condition. In a sick hemodynamically unstable patient PD/CVVH/CVVHD are possible. HD is possible only in a stable patient requiring quick and maximum solute clearance. However, no modality has been shown to be superior in improving the mortality and physician's confidence and experience determine to a large extent the choice of modality of dialysis.[1,2]

INDICATIONS OF DIALYSIS

1. Volume overload leading to gross edema/hypertension/congestive heart failure. It may be associated with minimal increase of BUN (blood urea nitrogen) and reasonable urine output (0.1-0.5 ml/kg/hr).
2. Hyperkalemia—In a cardiac patient serum potassium over 5.5 meq/L can be dangerous whereas neonates can tolerate high-levels of potassium.
3. Severe and increasing levels of BUN (relative indications on its own account)
4. Severe acidosis, hypo or hypernatremia.

Overall clinical picture and trend of clinical and biochemical picture determine the need for dialysis.[3] It is important to remember to dialyse early; to possibly avoid above mentioned problems.

PERITONEAL DIALYSIS (FIG. 65.2)

It can be done easily at all ages and practically in all clinical situations even in a patient who had abdominal surgery 3-4 days earlier. It is cheap, simple to perform and can be easily set up in a pediatric intensive care unit.[4]

Various types of PD catheters are available: Trocath (polyvinyl), Cook's catheter (polyurethane), Tenckhoff's catheter (silicone).[5] They are inserted with help of a trocar (Trocath) or via using a modified seldinger technique (Cook/Tenckhoff catheter). Peritoneum acts as a semi permeable membrane.

Fig. 65.2: Neonatal receiving peritoneal dialysis *(For color version see Plate 11)*

Insertion of Catheter

1. Adequate sedation is necessary. Use of pentazocine and midazolam or ketamine may be required in a fully conscious patient.
2. Confirm bladder is empty, if in doubt catheterize the patient.
3. Set up (Fig. 65.3.) PD Unit (2 PD bottles, Y giving set, drainage bag). In neonates where very small

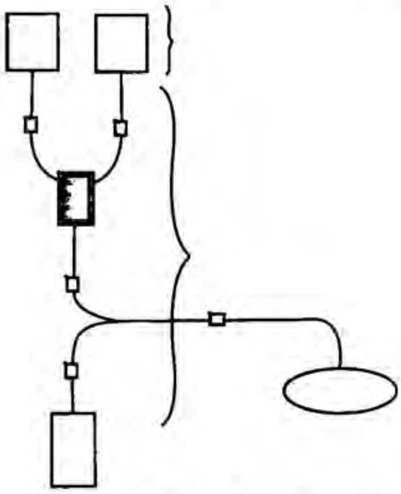

Fig. 65.3: PD set: Flow diagram

volumes may be required, pediatric burette set may be inserted in between the PD bottle and Y giving set. 1.35 to 1.5 percent concentration of peritoneal dialysis fluid (depending on glucose concentration) are available. If a large amount of ultrafiltrate is required, i.e. patient is grossly fluid overloaded, 25 or 50 percent glucose can be added to one of the PD fluid so as to increase glucose concentration to 3.5 to 4.5 percent. 1.35 to 1.7 percent PD bags are called as "light" PD bags whereas higher concentration PD bags are called as "heavy" PD bags. In each bag, to start with 500 units of heparin should be added. Some nephrologists add antibiotics for first 24-48 hrs (Vancomycin 25 mg/Liter and Amikacin 20 mg/L). In these doses antibiotics do not cause nephrotoxicity. Potassium chloride should be added only if serum K^+ is less than 5 mmol/L so as to create an equilibrium and to avoid hypokalemia. It is usually required once PD has been done for 6-12 hours. 3-4 mmol of KCl/Liter can be added to the PD fluid.

4. After cleaning and draping under sterile conditions catheter is inserted.In small children (<15 kg) insertion in flanks is preferred over subumbilical site (Fig. 65.4). Local anesthesia can be given depending on the clinical situation.
5. Abdominal cavity is filled with help of 16/18 guage intravenous cannula. The cannula is inserted in abdomen so as to go into the peritoneum and give free flow of PD dialysate into the peritoneal cavity. Normally cavity is filled with 20-40 ml/kg of PD fluid so as to distend the abdomen.
6. A small incision with blade is made and catheter is inserted with help of trocar or by modified seldinger technique. Catheter is either directed behind the urinary bladder or in one of iliac fossa. Correct position of catheter shall allow free flow of dialysate inside abdominal cavity as well as drainage outside to the drainage bag. Catheter is kept in position by applying purse string sutures.
7. 20 to 50 ml/kg of dialysate is infused in each cycle. Initially no dwelling is done, i.e. fluid is allowed to go in and as soon as required amount has gone in, drainage is allowed immediately. These cycles can be initially done half hourly and gradually interval is increased to one to two hours.
8. Dwelling is allowed after 6-8 flushing cycles (filling and immediate filling drain). Dwelling cycles are usually done over 1 hour (filling time is usually 5-10 minutes, 25-30 minutes is dwelling time during which exchange takes place and the rest, i.e. 25-30 minutes are given for drainage) Alternative light and heavy bags fluid is used so as to maintain peritoneal semipermeability.
9. Strict PD cycle chart is maintained. In and out fluid measurement determines how much fluid balance has been achieved (Negative balance—if fluid is removed from the patient, Positive balance—if fluid removed is less than given in). PD balance shall give accurate achievement of ultrafiltration and serum biochemistry gives clues about solute clearance. PD should be done continuously and gradually withdrawn only when kidney recovers. The whole process can also be done with an automated cycling machine.

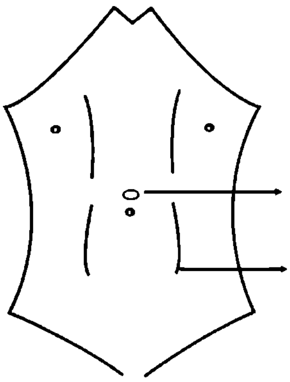

Fig. 65.4: Sites of peritoneal dialysis

Advantages of PD

It is cheap, easy to perform, can be done at bedside, can be done in a hemodynamically unstable patient as fluid solute are removed slowly. It can be done in any age group, even in a premature infant.

Disadvantages of PD

As fluid enters the peritoneal cavity it can cause respiratory embarrassment by pushing the diaphragm up especially in a child with respiratory distress. In a mobile child it restricts child's activity and mobility as the child has to be confined to bed in acute peritoneal dialysis. It can be unreliable as ultrafiltration can not be predicted. Catheter blockage or leakage can result in drainage failure. Fluid and solute removal can be inadequate especially in hypercatabolic states, sepsis, extensive trauma, etc. Uremia can persist for several days. The most serious complication is infection, i.e. peritonitis. Strict asepsis should be maintained while changing PD bags and touching PD catheters. All joints of PD bag, Y set, drainage bag and catheter should be sealed with betadine soaked gauzes.

HEMODIALYSIS (Fig. 65.5)

This modality is easily available in most adult renal units and same circuit along with smaller dialyser can be used in children over 15 kg weight. For smaller children dialysis machine with capacity of lower blood flow rate along with smaller pediatric circuit and dialyzer are required. In this modality the artificial kidney called the dialyser is used which acts as a semipermeable membrane (Fig. 65.6).

Double lumen vascular access is needed for hemodialysis. 8F/9F central lines are used in children with weight 15-25 kg and in older children 11F/12F catheters can be used. These catheters are placed by modified seldinger technique preferably in internal jugular vein (orsubclavian vein). Femoral vein can be used but infection rates are higher in this type of vascular access and in addition it restricts the child's mobility. There are two compartments in the dialyser. Blood passes through one compartment and dialysis fluid (unsterile fluid) passes through the other compartment in the opposite direction. The blood and dialysis fluid (Hemodialysis fluid) do not come in contact with each other at any stage. The blood flow is maintained at 5-10 ml/kg/min (100-150 ml/min) whereas dialysis fluid flows 7.5-20 ml/kg/min (max 1.5 times of blood flow). This transmembrane pressure (TMP), i.e. pressure difference between the dialysate compartment and blood compartment allows the water to move. TMP is positive in blood compartment. The ultrafiltration and solute clearance occur both via diffusion and convection. Usually the dialysis lines are primed with blood or 20 percent mannitol in first one or two dialysis cycles so as to avoid sudden osmotic disequilibrium or hypotension. In order to avoid clotting, heparin is used 30-50 U/kg as a bolus dose and further 20 to 30 U/kg is given after 1st and 2nd hours of dialysis so as to maintain anticoagulation (INR 1.5 to 2.0 times of normal). By experienced staff heparin coagulation free dialysis can also be done. For first time dialysis is done for 2 hours and subsequently for 3 to 4 hours depending on volume status of the patient. It is usually required three times in a week or more as per desired goals. The size of dialyser, i.e. surface area of the membrane should be approximately 0.7 of the total surface area of patient. By using large dialyser, increase of TMP, increase blood flow clearance and ultrafiltration can be increased. However, all of these factors can also

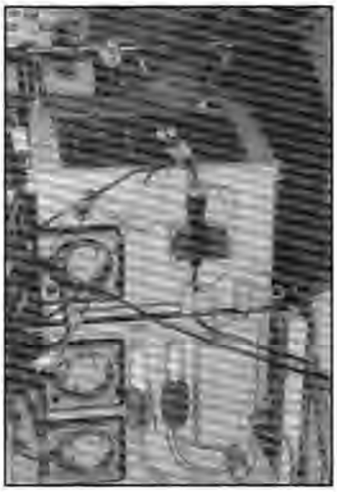

Fig. 65.5: Hemodialysis and hemodiafiltration equipment

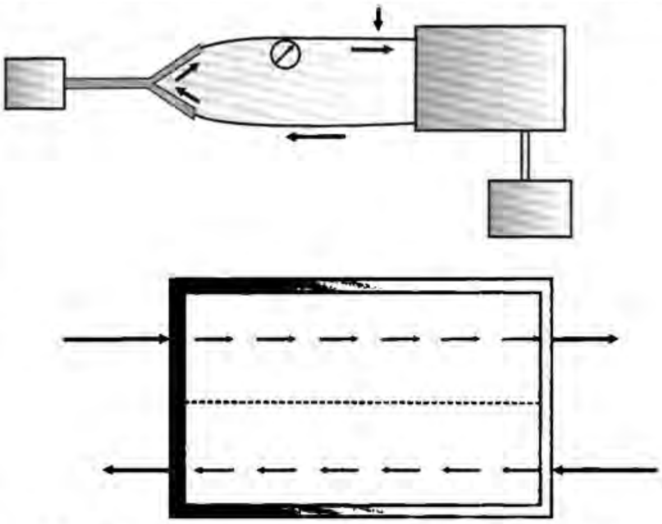

Fig. 65.6: Hemodialysis and dialyser: Flow diagram

cause sudden disequilibirium resulting in vomiting, convulsions, hypotension, etc.

Advantages of HD

There is maximum quick solute clearance especially for life-threatening hyperkalemia. Limited time for dialytic modality is needed, i.e. 2 to 4 hours on the day of dialysis.

Disadvantages of HD

Infection, coagulation problems, and difficult vascular access are main disadvantages. Also HD causes sudden disequilibrium due to volumes hifts and hence, it can't be done in a hemodynamically unstable patient. It is also difficult to do in small infants as sufficient blood flow cannot be obtained.

CONTINUOUS VENOVENOUS HEMOFILTRATION AND HEMODIAFILTRATION (CVVH/CVVHD)

This is the most physiological method of dialysis which mimics kidney function closely.[6,7] It is possible to do CVVH in a child over 4 kg weight. Hemofilters (HF) are made up of biocompatible synthetic materials such as polysulfone, polyamide, polyacrylonitrite. These membranes are very porous and allow large amount of fluid to be shifted through the hemofilter. This convective transport causes solute molecules to come along with it and hence, clearance occurs. However, in CVVH large amount of fluid is lost which is replaced by a hemofiltration fluid (HFF) or by physiological solution such as normal saline or ringer lactate (Fig. 65.7). The amount of HFF replaced is less than fluid which comes out through the hemofilter so as to create a negative balance in a fluid overloaded patient. Ultrafiltration mimics glomerular filtration, function of tubular reabsorption is replaced by HFF. HFF is replaced prior to HF, i.e. even before ultra-filtration has occurred so as to help to avoid clotting. For good solute clearance ultrafiltration of approx. 500 ml/sq meter surface area of patient/hour is required.

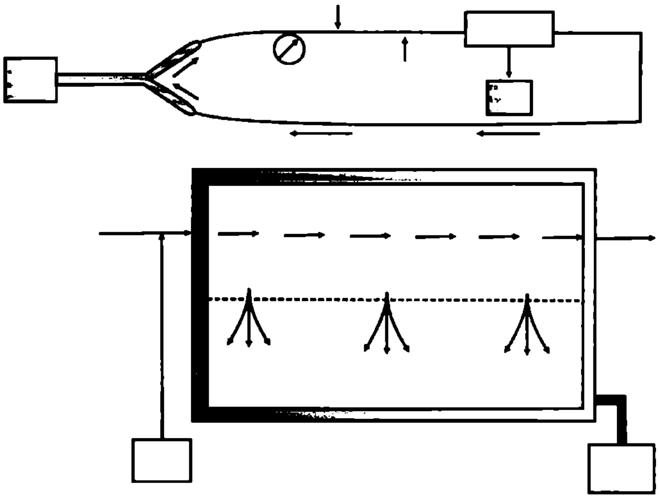

Fig. 65.7: Schematic flow diagram of continuous venovenous hemofiltration

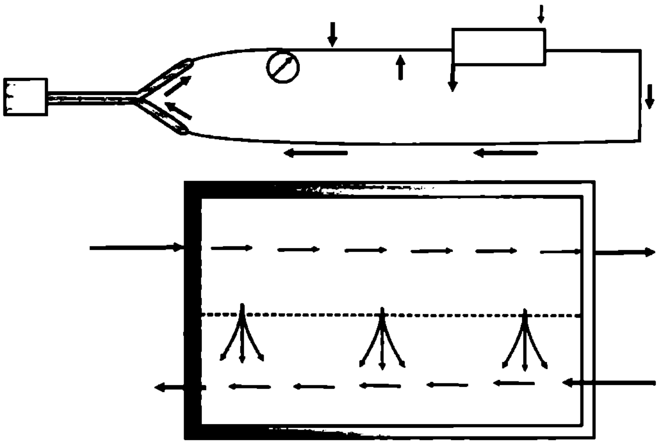

Fig. 65.8: Schematic flow diagram of continuous venovenous hemodiafiltration (CVVHD)

This modality is further modified to improve clearance by using sterile dialysis fluid (c.f. Hemodialysis fluid which is unsterile) instead of HFF. This method is called CVVHD (Fig. 65.8). Both convection and diffusion help to do clearance in CVVHD c.f. CVVH where only convection transport is at work. Like normal kidney CVVH/CVVHD is a continuous process throughout the period till goals are achieved. Filters and circuit may need to be changed after 48-72 hours. A blood pump is used to pump out blood from venous end. To avoid clotting of the circuit ACT (activated clotting time) should be between 160-200 sec when checked at the post-filter limb. Majority of these patient may have DIC, hence may not require anticoagulant, otherwise Heparin 5-20 units/kg stat followed by 5 units/kg/hr is given. Some nephrologists prefer to use sodium citrate as local circuit anticoagulant with replacement with calcium gluconate after filtration.

Advantages and Disadvantages of CVVH/CVVHD

CVVH and CVVHD are most physiological modalities and can be used in a hemodynamically unstable patient. It also removes cytotoxins and cardiotoxic factors so as to decrease peripheral resistance and increase cardiac output hence, giving further benefit to the patient. It gives continuous control of fluid status, electrolyte, acid-base balance. It is highly reliable. However, it is expensive, needs trained and dedicated staff, especially CVVH being a slow process, removes solute very slowly. Vascular access, bleeding, clotting of circuit are other problems. In control studies CVVH and CVVHD have not been shown to improve patient survival (cf. PD, HD) although RRT is now being given to much more sicker children since advent of CVVH and CVVHD.

Because of cost, in India there has been limited experience in children. Ideally in a tertiary health care center providing care for sick children all modalities of dialysis should be available. Depending on clinical situation one or more dialytic therapy may be required for a child with ARF. Also expertise should be developed so as to minimize complications. A unit should get used to all modalities of dialysis in children. Tertiary care center should be fully equipped to offer RRT including dialysis and should be able to look after children with ARF however, small they may be and whatever may be the clinical situation. It should be unacceptable for a child to die because of unavailability of RRT/dialysis.

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CHAPTER

66

Pediatric Renal Transplantation

Mukta Mantan, Arvind Bagga

Renal transplantation is standard therapy for patients with end stage renal disease (ESRD) in children. It is usually an elective surgical procedure as most of donors are live donors rather than cadeveric donors. Inputs from the pediatric nephrologist, transplant surgeon and pediatric intensivist are imperative in providing optimum perioperative care to the transplant recipient.

Units involved in renal transplantation usually have detailed protocols on pre and postoperative care of donors and recipients. These protocols are updated regularly depending on the prevailing standards of therapy.

Immediate Preoperative Period

Most patients of ESRD are on maintenance dialysis prior to transplantation. The need to dialyze the patient immediately before transplantation is guided by the presence of fluid overload, hyperkalemia and day of last dialysis. Most centers prefer to dialyze patients on the evening prior to transplantation, mainly to prevent hyperkalemia. It is essential to maintain serum potassium levels below 5.5 mEq/L to prevent arrhythmia during anesthesia and surgery. The incidence of preoperative hyperkalemia is as high as 20-38 per cent in various studies. Potassium binding resins can be administered orally or rectally to prevent this complication.

Significant volume reduction should be avoided during dialysis to prevent intraoperative hypovolemia. Long standing uremia can cause platelet dysfunction resulting in excessive bleeding during surgery. Regular dialysis preoperatively can ameliorate this abnormality. While anemia can lead to complications during surgery, blood transfusions should be limited in the preoperative period to prevent alloimmunization and the risk of graft rejection. Transfusions can be given if necessary during surgery. A hematocrit level above 35 percent is acceptable. Most patients undergoing transplantation are on treatment with the hormone erythropoietin, which maintains hematocrit in this range.

A detailed clinical examination should be done to ensure fitness for surgery. Fresh crossmatch of patient sera for anti HLA antibodies, against donor mononuclear cells, is done by flowcytometry or ELISA 1-2 days prior to the surgery. Two units of blood are arranged from the blood bank. A chest X-ray is done to rule out any infection or fluid overload and electrocardiogram for arrhythmia. Urinalysis and culture are obtained 2-3 days before transplantation. Blood samples are taken for complete blood counts, electrolytes and blood gases prior to surgery. Estimation of bleeding time, clotting time and prothrombin time is also necessary. Consent from the prospective donor and recipient is taken on appropriate forms.

Surgery

In infants and young children the allograft is placed intra-abdominally. The renal artery is connected to the aorta and renal vein to the inferior vena cava. In older children the graft is placed in the iliac fossa and the renal artery and vein are connected to common or external iliac artery and vein respectively. Advancements in the vascular techniques have decreased the incidence of allograft loss due to vascular thrombosis. The ureter is anastomosed to the bladder using uretero-neocystostomy. The arterial supply of lower ureteric segment should be preserved as ischemia here can cause ureteral obstruction or urinary leaks. With stringent aseptic practices and use of perioperative antibiotics, wound infections have become uncommon.

Pre-transplant native kidney nephrectomy/ nephroureterectomy is no longer a routine procedure. The native kidneys are left in place because they still may produce significant volumes of urine, secrete erythropoietin and convert vitamin D to its active metabolites. Unilateral or bilateral nephrectomy/nephroureterectomy is done in specific instances, such as large polycystic kidneys, significant proteinuria, poorly controlled hypertension and chronically infected kidneys.

Intraoperative management includes appropriate fluid therapy and administration of immunosuppressive drugs, diuretics and antibiotics. Good hydration is important to ensure adequate blood flow to the allograft. A sluggish flow can promote its thrombosis and acute tubular necrosis. The central venous pressure (CVP) should be monitored and maintained between 10-12 cm of water during and after surgery. A good peripheral venous access should be established to deal with copious fluid replacement. Mannitol (0.5 g/kg) is given intravenously in the theatre before the arterial clamp to donor kidney is released followed by intravenous frusemide at a dose of 1-2 mg/kg. This causes brisk diuresis and prevents graft ischemia. The appearance of the renal allograft after completion of the anastomosis, and release of vascular clamps should be recorded in the notes. Intraoperative perfusion characteristics of the graft and intraoperative urine volume are good predictors of graft function.

Postoperative Period

The transplant team should evaluate the patient on arrival from the operating room. The initial assessment should include hemodynamic and respiratory stability. Most patients are awake and extubated.

The primary goal during immediate postoperative period is to promote and maintain renal perfusion and diuresis. This is achieved by administration of a combination of crystalloid and colloid solutions to replace urine output, insensibl losses and gastrointestinal and third space losse The patient requires close hemodynamic monitorin and meticulous fluid management in an intensiv care unit. Routine monitoring and evaluation durin the first 48 hours is shown in Table 66.1.

Fluid Management

It is desirable to maintain adequate hydration t prevent hypovolemia and graft dysfunction. Th CVP should be maintained at 10-12 cm of water Careful monitoring of heart rate and blood pressur also detects any hypovolemic episodes. A detaile record of urinary output and drain volumes i maintained. Pediatric recipients of adult kidne frequently produce large volumes of urine durin immediate post-operative period. A high urine flow (over 2 ml/kg/hr) is expected in the first 48 hours Urine output is replaced with 5 per cent dextrose i 0.45 per cent saline and 10 ml sodium bicarbonat per liter, on a volume for volume, hourly basis. Insensible water losses are electrolyte free, and are replaced with 5 per cent dextrose solution. Blood loss incurred during and after surgery is also replaced. Maintenance potassium is added when serum potassium falls below 3.5 mEq/L.

Maintaining adequate systemic pressure is imperative, since, the allograft is very sensitive to even brief episodes of hypoperfusion. Dopamine is infused at a rate of 5-8 µg/kg/min to maintain a mean arterial pressure above 80 mmHg. The rates of infusion can be increased to 10 µg/kg/min. While low dose dopamine is frequently used in a number of transplant units, for the first 48 hours, the benefits of this practice are controversial.

Table 66.1: Monitoring of transplant recipients during first 48-72 hours

- Urine output every 30 minutes and then every hour
- Blood pressure every 30 minutes for first 6 hour, every hour for 24 hour, then 6 hour
- CVP* every hour for initial 12 hour, then 4-6 hour
- Temperature hour for initial 4 hour, every 6 hour subsequently
- Weight once a day
- Hemoglobin and complete counts daily
- Blood sugar, urea, creatinine, electrolytes, calcium, phosphate, bicarbonate 12 hour

*CVP-Central venous pressure

In patients having *oliguria* after the surgery, if the urine volume is below 2 ml/kg/hour and CVP measures above 12 cm then a single dose of frusemide (1 mg/kg) is given. If the CVP measures below 10 cm, a bolus of 10 ml/kg normal saline or 5-10 ml/kg 5 percent albumin is administered. Besides the CVP, clinical status and chest X-ray are also good measure of volume overload. If the renal functions are deranged and urine output is decreased, then the fluid is administered as insensible water losses (400 ml/m^2) plus the urine output.

Polyuria (urine volumes of > 4 ml/kg/hr) can result in dyselectrolytemia. For these patients only 50-75 per cent of the output is replaced every hour. If urine flow rates are more than 8 ml/kg/hr, then the dextrose content of replacement fluid should be reduced to 2.5 percent. This replacement is continued for first 48 hours. If hyperglycemia or glucosuria occurs, plain insulin can be used as an intravenous drip or intermittent subcutaneous boluses (one unit of plain insulin neutralizes about 3-4 g of dextrose). Hypocalcemia may also occur and should be monitored closely. Urinary phosphate wasting often results in hypophosphatemia. Phosphate supplements (Joulie's solution) should be given if serum phosphate levels are below 3.5 mg/dL. After 48 hours if the kidney function tests are normal, the fluids are reduced to half of the urine output. By day 3 to 5 most children with satisfactory graft function do not require intravenous replacement of urinary fluid losses. Fluid requirements are met with ad-lib administration of oral fluids.

Hypertension is common in the immediate post-transplant period. The etiology is multifactorial and includes pre-existing hypertension, volume overload, and medications like steroids and cyclosporin. Hypertension can be managed with the use of calcium channel blockers like nifedipine (2.5-5 mg sublingually). If the hypertension persists, then sustained release preparation of nifedipine (0.5-2 mg/kg daily) or amlodipine (0.1-0.5 mg/kg/day) are recommended. Other medications that can be used are beta-adrenergic antagonists like atenolol (1-2 mg/kg/d), alpha-receptor blocker prazosin (0.1-0.4 mg/kg/d) or a central adrenergic agonist clonidine (10-40 μg/kg/d). ACE inhibitors should be avoided in the immediate post-transplant period as they may decrease the perfusion of the allograft.

Complications

Impaired graft function frequently complicates the initial post-transplant period. Early non-function with oligoanuria chiefly reflects pre-transplant events that have compromised graft function. These include hypovolemia in the donor or recipient, unrecognized recipient immunity against donor tissue, or complications of the surgical procedure.

Oligoanuria in the immediate post-transplant period should be thoroughly evaluated. All pre and post-renal causes should be excluded. Decreased intravascular volume is the chief pre-renal cause of graft dysfunction. Common causes of early graft dysfunction are shown in Table 66.2. Pre-renal dysfunction is managed with administration of intravenous fluid boluses and is usually reversible.

Hematuria is an expected consequence of ureteral transplantation and, if associated with poor urinary flow can result in clot formation and obstruction of urinary catheter. Catheter obstruction also increases intraluminal pressure in the bladder, thereby threatening the ureteral anastomosis. Bladder catheter should be irrigated, flushed and if necessary changed. If this does not alleviate the oliguria or gross hematuria, a renal ultrasound should be done to rule out ureteral obstruction and/or dilatation of the pelvis. Presence of ureteral obstruction may require surgical intervention. If oligoanuria persists despite these measures acute tubular necrosis (ATN), and arterial or venous vascular thrombosis should be suspected.

ATN commonly occurs due to persistent hypovolemia or prolonged cold ischemia time. This is usually reversible.

Vascular thrombosis is usually a result of unsatisfactory surgical technique. *Clinically such a patients will present*

Table 66.2: Causes of early allograft rejection

- Hypovolemia
- Acute tubular necrosis
- Hyperacute, acute rejection
- Catheter obstruction
- Arterial or venous thrombosis
- Urine leak

with graft tenderness, pain and decreased urine output. It is essential to evaluate all patients of oligoanuria with an ultrasound Doppler and a radionuclide renal scan. Doppler helps in differentiating a vascular obstruction from an episode of rejection or urinary leak. If the flow study reveals no demonstrable blood flow to the graft, a prompt surgical re-exploration is necessary. A majority of these grafts would finally be lost and patients revert back to hemodialysis. In presence of a good vascular flow a diagnosis of delayed graft function is entertained. Hematomas and lymphocoeles may develop after the surgery and impinge on the allograft vessels or the ureters causing impaired function. Post-surgical bleeding is usually managed conservatively, with blood and blood products, and does not require re-exploration on most occasions.

Hyperacute Rejection

Hyperacute rejection occurs due to preformed cytotoxic antibodies in recipient against donor class I or II HLA antigens. These antibodies bind to the endothelial surfaces of the arterioles on the graft, activate complement, and lead to severe vascular injury, including graft thrombosis and obliteration of graft. It manifests with fever, rapid development of dysuria, graft tenderness and swelling within first week of transplant. Apart from radiological investigations, a renal biopsy is of significant help in diagnosing hyperacute rejection. Blood levels of panel reactive antibodies (PRA) level are high in such patients. The availability of modern crossmatching techniques has greatly reduced the incidence of hyperacute rejection. In case of a rare occurrence, the patient may be treated with pulse methyl-prednisolone (30-40 mg/kg/day) for 3 days. Besides steroids, other immunosuppressive agents like monoclonal (OKT3) and polyclonal antibodies (anti-thymocyte and antilymphoblast globulins) have been used for treatment of rejection. These antibodies bind to various T cell receptors, leading to their inactivation. Administration of monoclonal antibodies against interleukin-2 receptors (basiliximab, daclizumab) may be useful in some cases. Intravenous immunoglobulins and plasmapheresis have also been recommended for the treatment of episodes of rejection, which are resistant to the above therapies.

Acute Rejection

Acute rejection is the main cause of allograft dysfunction in the first post-transplant year. It may be seen at anytime post-surgery but most commonly in the first six months. Most episodes of acute rejection are predominantly cell mediated and are reversible with appropriate treatment. Patients often present with fever, deranged renal functions, graft tenderness and oliguria. The differential diagnosis includes urinary tract infections, cytome-galovirus infection and cyclosporin toxicity. Besides infection screen and cyclosporin blood levels, an ultra-sound Doppler and a nuclear scan often help in distinguishing between these conditions. Graft biopsy is however essential to establish the diagnosis of rejection. About 75 per cent of these rejection episodes reverse on treatment with methyl-prednisolone. Treatment with monoclonal antibodies (OKT3) is recommended for treatment of patients who do not respond to treatment with steroids.

Other Complications

Patients should be ambulated by 24-48 hours and should start on a liquid diet by the third day. Mild to moderate pain may occur at the incision site in the first week. Severe pain or absence of bowel sounds by 48-72 hours should be investigated to exclude rejection, perinephric hematoma and urinary leak. Fever in the first week could be due to postoperative complications like atelectasis, wound, urinary tract or central line infections. More than 90 percent infections during the first post-transplant month are due to problems related to surgery, drains and catheter.

Most *opportunistic infections* are uncommon during this period and usually *occur beyond the first 2 months of surgery.* These include infections due to cytomegalovirus and Ebstein-Barr virus, mycobacteria and pathogenic protozoa; *Toxoplasma* and *Pneumocystis* are the commonest protozoal infections. These patients are also more predisposed to fungal infections including cryptococcosis and aspergillosis.

Diagnosing these infections is often difficult due to concomitant immunosuppression; a high index of suspicion is thus necessary.

Immunosuppression

Most centers follow an immunosuppression protocol comprising a combination of steroids, azathioprine and cyclosporin, however, immunosuppression may require modification in different patients. Immunosuppression is begun 12 hours prior to the transplant with oral cyclosporin and azathioprine at doses of 7.5 mg/kg and 5 mg/kg respectively. Intravenous methylprednisolone is infused at doses of 10 mg/kg (diluted in normal saline and given over 20-30 minutes), two hours prior to the surgery. The next dose of cyclosporin and azathioprine is administered 6-8 hours following surgery. Therapy with oral prednisolone is started from the next day at doses of 2 mg/kg/day, which is gradually tapered to about 0.4 mg/kg/day by the end of first month. Cyclosporin is administered at the dose of 10-12 mg/kg/day for the first fortnight and then tapered to 8-10 mg/kg/day over the next two weeks. Azathioprine is continued at doses of 1-1.5 mg/kg/day. Some centers prefer to use tacrolimus, another calcineurin inhibitor instead of cyclosporin. Mycophenolate mofetil (MMF) has replaced azathioprine in most transplant centers in the developed countries. This drug is a more specific inhibitor of lymphocyte proliferation and has less bone marrow toxicity. Randomized trials have shown that the use of tacrolimus and MMF is superior to cyclosporin and azathioprine respectively in the prevention of acute rejection episodes and chronic allograft nephropathy.

Monitoring

Urine output is carefully monitored during the first 3-4 days of surgery. The bladder catheter is usually removed after 48 hours. Vitals are initially monitored every 30-60 minutes and then 2 hourly. The central venous pressure is initially measured hourly and then 6 hourly. If blood pressure and urine output is normal, the CVP catheter is removed after 48-72 hours. A rise of body temperature may occur because of infection or rejection. Blood levels of urea, creatinine, sodium, potassium, calcium, phosphate, hemoglobin and counts are measured every 12 hours initially and then once daily. A blood cyclosporin level (C2 level or trough) is done at the end of first week. The accepted 12-hour trough levels of cyclosporin are between 250-300 ng/ml in the first two transplant months. Recently peak drug levels (C2), 2 hours after oral dosing are measured at many centers. These levels correlate better with drug exposure as compared to trough levels and the accepted target levels in the first two months of transplant vary between 1500-2000 ng/ml. The trough levels vary with the methodology of testing. High performance liquid chromatography (HPLC) is the most specific method to measure the unmetabolized drug. Other methods like radioimmunoassay and enzyme linked immunoabsorbent assay are cheaper and easier to perform though they overestimate the drug levels by almost 20-30 percent. A DTPA scan is done to assess graft function after 72 hours. If there are no complications in the post-operative period, most patients are ready for the discharge by the second week of surgery.

After discharge, graft function should be assessed at least thrice weekly for 2 weeks, twice weekly and weekly for a month each, and then at monthly intervals.

Other Medications

Antibiotic prophylaxis with cephalosporins is given for the initial 3-5 days. Urinary prophylaxis with cotrimoxazole (2 mg/kg trimethoprim) is begun when the serum creatinine falls below 1.5 mg/dL and is continued for three to six months; this also prevents opportunistic infections with *Pneumocystis* and *Toxoplasma.* Oral antifungal prophylaxis with nystatin/fluconazole is also given during this period. Pain is relieved using paracetamol. Prophylaxis against acid peptic disease is provided with histamine-2 receptor blockers or proton pump inhibitors for 1-2 months. Ganciclovir prophylaxis for cytomegalovirus disease is usually reserved for high-risk patients (donor positive; recipient negative serology). The prophylaxis for such patients is given intravenously with ganciclovir for the first 2 weeks and then orally either ganciclovir or valganciclovir for 3 months.

Survival

Over last ten years, there has been gradual but steady improvement in graft survival. Cadeveric transplant survival is 88 percent at one year and 60 percent at the end of 10 years while comparable rates from living donor transplants are 9 and 70 percent respectively.

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Section Five

Gastroenterological Issues

CHAPTER

67

Gastrointestinal Bleeding: Diagnosis and Management

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The diagnostic approach in a patient with suspected gastrointestinal (GI) bleeding requires a careful history, physical examination and the performance of appropriate tests. Initially, it must be documented that the patient has infact bled. Second, the severity of bleeding must be determined. Thirdly, a distinction must be made between upper and lower (proximal or distal to the ligament of Treitz) tract bleeding. Finally, the specific site must be identified. In cases with acute massive gastrointestinal bleeding management consists of initial stabilization first followed by the diagnostic workup to determine the site and exact cause of bleeding, and finally the definitive treatment of the cause of bleeding.

Assessment of the Severity of Bleeding

The severity of the GI bleeding can be delineated by the parent or patients estimate of the volume of blood lost, and the clinical presentation. Since parents often exaggerate the quantity of blood lost, the physician should request whether it was a drop, a spoonful, a cupful or more. Bright red rather than coffee ground hematemesis points to a rapid rate of bleeding. Coffee ground material has been denatured by gastric acid and usually indicates a low rate of bleeding. The estimated volume of blood loss should be correlated with the clinical status of the patient. Low blood pressure, orthostatic changes, tachycardia, severe pallor, poor capillary and venous filling, sweating, restlessness, and mental confusion all suggest significant blood loss and demand immediate measures. Perhaps the best indicator of significant acute blood loss is postural changes in pulse and blood pressure. A drop in systolic blood pressure of 10 mmHg or more, or an increase in 20 beats/min in pulse on moving the patient from supine to sitting position suggests significant blood loss. It must be remembered that hematocrit may be normal or only slightly decreased, because of a delay in hemodilution after acute blood loss.

Establishing the Level of Bleeding

Gastrointestinal bleeding is categorized as upper, if above the ligament of Treitz and lower if distal to the ligament of Treitz. In the majority of cases, the clinical presentation together with nasogastric lavage will delineate the level of bleeding within the GI tract.

Hematemesis strongly suggests a bleeding site above the ligament of Treitz. The absence of hematemesis however, does not eliminate an upper GI source. The cathartic action of blood may cause an acute upper GI bleed to present as melena or rarely gross maroon colored clots. Melena usually indicates bleeding above the ileocecal valve, and is related to the effects of digestive enzymes or bacterial action on intraluminal blood. In general, the darker blood, the higher as it originates in the GI tract. Rarely a bleeding source in the right colon may present with melena, if there is delayed colonic transit.

Hematochezia, or the passage of gross blood per rectum, usually means bleeding distal to the ligament of Treitz. Bloody diarrhea usually reflects colonic bleeding. Streaks of bright red blood on the outer stool or blood alone following a bowel movement points to the perianal area or rectum. The rectal passage of a currant jelly-like substance indicates vascular congestion and hyperentension as seen with an intussusception involving the distal, small or large bowel.

All patients in whom the level of GI bleeding is not obvious should have a nasogastric tube passed, and their stomach aspirated. This assists with not only categorizing the bleeding but also provides a visual estimate of the amount of bleeding.[1,2] The presence of blood in the stomach is diagnostic of an upper GI bleed. It is important to realize however, that the absence of blood in the aspirate does not exclude a duodenal source distal to a competent pylorus or a gastric source which has ceased bleeding. Nevertheless, in a study of 1000 patients with GI bleeding, only 1 percent with upper GI bleeding had a gastric aspirate negative for blood. A few streaks of blood in the stomach may be secondary to trauma caused by passage of the tube, and should not be taken as evidence of upper GI tract bleeding without supportive evidence.

Identification of the Specific Site

Information from the history, physical examination and laboratory tests should lead to the formation of a limited differential diagnosis, and an appropriate strategy of intervention. Specific endoscopic and radiologic diagnostic procedures are rarely indicated emergently in the evaluation, but the subsequent filming and sequence of these tests is critical. Knowledge of the most common causes of bleeding in a given age group can assist in the formation of a rapid limited differential diagnosis and guide in the selection of tests. Tables 67.1 and 67.2 list the age related causes of upper and lower GI bleeding respectively.

The majority of cases of upper GI bleeding can be classified into two diagnostic categories: mucosal lesions and esophageal varices (Table 67.1). Mucosal lesions include esophagitis, gastritis, MalloryWeiss tears, stress ulcers and peptic ulceration. Although lesions in both categories may be present with severe bleeding, bleeding from mucosal lesions is usually self limiting and will respond to conservative medical management. Bleeding from esophageal varices usually stops spontaneously but recurs and requires more aggressive therapy. The object of the history, physical examination and laboratory tests is to distinguish between these two categories. A history of recent significant stress, chronic medication usage or recurrent vomiting and abdominal pain is suggestive of a mucosal lesion. A normal physical examination with the exception of mild to moderate periumbilical or epigastric tenderness is common. Mucosal lesions may be associated with antecedent occult bleeding, resulting in a low mean corpuscular volume on initial blood count. A history of jaundice, hepatitis, blood transfusions or a significant illness associated with portal vein thrombosis, i.e. sepsis, shock, umbilical vein catheterization in the neonatal period, raises the possibility of bleeding from esophageal varices. Signs of chronic liver disease, hepatomegaly, splenomegaly, and ascites should be

Table 67.1: Etiology of upper gastrointestinal bleeding based on age

Neonatal period (< 4 wk)	Infancy (< 2 yr)	Preschool	School age
1. Bleeding diathesis	1. Stress ulcer[a]	1. Stress ulcer[a]	1. Chronic peptic ulcer
2. Hemorrhagic gastritis	2. Esophagitis[a]	2. Gastritis[a]	2. Stress ulcer[a]
3. Stress ulcer[a]	3. Gastritis[a]	3. Mallory-Weiss tear[a]	3. Gastritis[a]
4. Swallowed maternal blood[a]	4. Malloy-Weiss tear[a]	4. Esophageal varices	4. Mallory-Weiss tear
5. Esophagitis[a]	5. Pyloric stenosis	5. Esophagitis	5. Esophageal varices
6. Foreign body irritation (nasogastric tube)	6. Vascular malformation	6. Foreign body	6. Esophagitis
7. Vascular malformations	7. Duplication	7. Vascular malformation	7. Inflammatory bowel
8. Duplication		8. Hemobilia	8. Vascular malformation
			9. Hemobilia

[a]Indicates most common causes of bleeding in a given age group[9]

Table 67.2: Etiology of lower gastrointestinal bleeding based on age

Neonatal period	*Infancy*	*Preschool*	*School age*
Well infant			
1. Swallowed maternal blood	Anal fissure[a]	Infectious colitisa	Infectious colitis[a]
2. Infectious colitis[a]	Infectious colitis	Juvenile polypsa	Inflammatory bowel[a]
3. Milk allergy[a]	Milk allergy[a]	Anal fissure	Pseudomembranous enterocolitis
4. Hemorrhagic disease	Nonspecific colitis	Intussusception	Polyps
5. Duplication of bowel	Juvenile polyps	Meckel's diverticulum	Angiodysplasia
6. Meckel's diverticulum	Intussusception	Angiodysplasia	Hemolytic-uremic syndrome
Sick infant			
7. Necrotizing enterocolitis	Meckel's diverticulum	Henoch-Schonlein purpura	Hemorrhoids
8. Infectious colitis[a]	Duplication	Hemolytic-uremic syndrome	Ischemic colitis
9. Disseminated coagulopathy	Hemolytic-uremic	Inflammatory bowel disease	
10. Midgut volvulus[a]	Inflammatory bowel disease	Pseudomembranous enterocolitis	
11. Intussusception	Pseudomembranous enterocolitis	Ischemic colitis	
12. Congestive heart failure	Ischemic colitis		

[a]Indicates most common causes of bleeding in a given age group[9]

looked for on examination. Laboratory studies may reveal leukopenia and thrombocytopenia from hypersplenism and or abnormal liver enzymes, bilirubin, albumin and coagulation studies.

Further Diagnostic Evaluation

The major diagnostic alternatives in the further evaluation of upper GI bleeding include fiberoptic endoscopy, and double contrast radiography. Selective abdominal arteriography and surgery are rarely required to make a diagnosis, since the introduction of fiberoptic endoscopy which allows for almost complete internal visualization of the upper GI mucosa.

The main advantage of fibroptic endoscopy in upper GI bleeding include direct visualization of lesions which remain undetected by conventional contrast radiography, and application of therapeutic modalities such as sclerotherapy. In the pre-endoscopic era 20 to 50 percent of the bleeding sites remained unidentified, whereas most authors using fiberoptic endoscopes now report identification of more than 80 percent of the bleeding sites.[3,4] Although the diagnostic capabilities of the procedure are recognized, obtaining a more precise diagnosis in previous studies did not seem to influence the requirements for blood transfusion or to decrease the mortality rate from upper GI bleeding.[5] These conclusions may be challenged however, as more experience is gained with the use of sclerotherapy, heater probes, and lasers in the pediatric population. Emergency endoscopy is usually reserved for the patient who continues to bleed at a rate considered life-threatening, and in whom a precise etiologic diagnosis will lead to specific endoscopic or surgical therapy. Elective endoscopy is performed 12 to 24 hours following admission in patients who stop bleeding spontaneously, but who require transfusion in hematocrit below 30, or have a history of previous unexplained upper GI bleeding episodes. Although barium contrast has no diagnostic usefulness in the presence of active bleeding, all other patients who have stopped bleeding at the time of admission/or soon after, and who remain stable may be evaluated by air contrast-barium study. In addition, any patient with a significant bleeding episode resulting in a hematocrit lower than 30, and a normal endoscopy should undergo radiography to rule out a gastric or duodenal duplication which may not be appreciated on routine endoscopy.

LOWER GI BLEEDING

The majority of GI bleeding in the pediatric age population originates distal to the ligament of Treitz, and is self limiting. Furthermore, 70 to 80 percent of lower GI bleeding occurs in the anus, rectum, and colon. As noted in Table 67.2, age is a much more important diagnostic factor in lower GI bleeding.

The main priority for the physician in evaluating the patient with lower GI bleeding is to identify those patients with bleeding secondary to intestinal obstruction. Intussusception and midgut volvulus secondary to malrotation are the major types of intestinal obstruction. Recognition of these conditions, and other causes of intestinal obstruction resulting in compromise to the vascular supply is imperative to prevent significant morbidity.

As in patients with upper GI bleeding, the history, physical examination and appropriate laboratory tests will often distinguish between obstructive and non obstructive bleeding. In addition an initial flat and upright abdominal X-ray film may show signs suggestive of obstruction, i.e. absence of rectal air, dilated proximal loops of bowel, air fluid levels, or a mass effect. At any age the acute onset of abdominal pain, vomiting and distension associated with rectal bleeding is highly suggestive of intestinal obstruction. The occurrence of abdominal cramps accompanying rectal bleeding in an infant less than 2 years old should always be approached as intussusception until proven otherwise. The blood in this case is usually dark red (currant jelly stool). On physical examination, the presence, of abdominal distension, tenderness, a palpable mass, peritoneal signs or hyperactive bowel sounds should lead the clinician to request a flat and upright abdominal X-ray film to exclude an obstructive process during the initial evaluation.

Nonobstructive disorders associated with lower GI bleeding most often present with a history of diarrhea, constipation or painful bowel movements. Diarrhea, abdominal pain, and systemic symptoms such as fever and rash suggest an inflammatory lesion, the most common etiology being a bacterial or viral infection. In these cases, a high degree of suspicion must be maintained for other causes of inflammatory bowel disease, i.e. hemolytic uremic syndrome, Henoch Schonlein purpura, ulcerative colitis or Crohn's Colitis. Constipation, or the passage of either large or hard stools is commonly associated with the presence of an anal fissure. Pain on defecation is suggestive of an anal fissure, cryptitis or proctitis.

Lower GI bleeding in the absence of any other symptoms suggests a polyp, Meckel's diverticulum, or vascular anomaly. Meckel's diverticulum is the most common cause of severe lower GI bleeding in all age groups, even though 50 percent of symptomatic diverticula present before the age of 2 years.[6] Juvenile polyps are the most common type encountered in the pediatric population with a peak presentation in the 2 to 5 years age range. They frequently present with intermittent mild bright or dark red blood. Telangiectasias, angiodysplasia and hemangioma of the GI tract are rare causes of lower GI-bleeding in pediatric populations, but may be seen in patients with syndromes including Osler-WeberRendu, blue rubber nevus, and Ehlers-Danlos syndrome.

Physical examination with the possible exception of mild to moderate periumbilical or lower quadrant tenderness is usually benign in patients with nonobstructive disorders. Visual inspection of the perianal area, and digital rectal examination are mandatory to detect the possibility of an anal fissure, cryptitis or a rectal polyp. In patient with upper GI bleeding, examination of the skin is important, looking for evidence of a bleeding diathesis, ecchymosis, eczema, or, erythema nodosum, all clues to specific disorders.

Further Diagnostic Evaluation

Once an obstructive process is ruled out, subsequent evaluation of lower GI bleeding should follow a logical sequential approach. Since most cases are self limiting, the urgency and extent of the evaluation is determined by the amount of bleeding, age of the patient, associated clinical symptoms and physical findings.

An initial complete blood count can not only assess the amount of bleeding, but red cell indices may also give an indication of the chronicity of the bleeding. A smear of the stool, looking for white cells should be performed, along with cultures for routine bacterial pathogens and parasites in all patients with suspected infectious colitis. In those patients with minimal bleeding and who are otherwise well, observation alone until the culture results are available, is not unreasonable. In patients with more moderate or persistent bleeding, and a negative infectious evaluation, proctosigmoidoscopy is performed and if negative, colonoscopy can follow to visualize the whole colon and the terminal ileum.

The fiberoptic colonoscopes are superior to barium examination in bleeding of the GI tract, and allow for the use of therapeutic modalities including biopsy, electrocautery, and polypectomy.[7] Preparation of the colon is crucial to permit satisfactory visualization of the mucosa. Use of the poorly absorbed electrolyte polyethylene glycol solutions may permit rapid evaluation of the colonic contents with no complications. However, in most patients with diarrhea, no preparation is necessary. Sedation is preferable to general anesthesia, to limit the risk of perforation by allowing the patient to respond to increased pressure. If a source for the bleeding is not identified a Meckel's scan is performed for identification of functional gastric mucosa in an ectopic location, i.e. Meckel's diverticulum or duplication cysts of the GI tract. The agent used, technetium-99m pertechnetate, is injected intravenously and loosely binds to plasma proteins and accumulates in functional gastric mucosa including the stomach and ectopic locations. A Meckel's diverticulum often presents as an abnormal focal collection in the mid abdomen, or the right lower quadrant, a duplication cyst can be spotted anywhere in the abdominal field. Unfortunately, as many as 20 percent false positive or false negative results have been reported."

In the stable patient with a negative Meckel's scan, an upper GI with small bowel follow through (UGI SBFT) study with air contrast is subsequently performed to identify any small bowel lesion. Enteroclysis or a small bowel enema utilizing a nasogastric tube to obtain better delivery and therefore coating of the distal small bowel is the preferred method. This study may identify on ileal ulcer, or other lower GI lesion not seen on routine UGI SBFT.[8,9]

Patients with intermittent bleeding, and a negative colonoscopy and Meckel scan should undergo a bleeding scan. The radio nuclide imaging agents can detect bleeding at rates as low 0.1 ml per minute.[10] If a site is identified, further characterization of the site with endoscopy or angiography should be done in most cases. Angiography identified a bleeding site in approximately 75 percent of such children in one study.[11]

In the rare patient with unremitting lower GI bleeding requiring resuscitation and/or transfusion, exploratory laparotomy remains a reasonable approach.[12] Intraoperative endoscopy should be performed if no obvious lesion is identified on initial inspection of the serosal surface. The gastroscope or colonoscope is inserted, and the intestine is gradually telescoped over the endoscope by the surgeon while the endoscopist tries to identify mucosal lesions. Once again, it is important to emphasize that in massive rectal bleeding the pediatric gastroenterologist must always consider a duodenal bleeding site associated with a competent pylorus, leading to a negative nasogastric aspirate.

MANAGEMENT

Stabilization in the PICU

Although the majority of GI bleeding in children is self limiting, early recognition of the signs and symptoms of significant bleeding is imperative. This is especially important in younger infants and neonates in whom hemodynamic reserves and compensatory mechanisms are inadequate. Decreased systolic and pulse pressure, orthostatic hypotension, tachycardia, tachypnea, prolonged capillary refill or poor peripheral perfusion should alert the clinician to the possibility of a 20-25 percent blood volume loss.[13] Initial stabilization in these patients in hemorrhagic shock is directed toward preventing or treating hypovolemia, and restoring the hematocrit to acceptable levels to maintain oxygen delivery to tissues. Intravenous access with a large bore peripheral line is critical, especially in the apparently stable patient in whom shock may be delayed. Patient should be transferred to the PICU and a central line access should be obtained for monitoring of CVP and fluid therapy. An initial fluid bolus of 20 ml per kilogram is given over ten minutes after initial blood studies including type and cross match, complete blood count, platelet count prothrombin time, and partial prothrombin time are obtained. The choice of fluid for intravenous bolus remains controversial, but most clinicians prefer crystalloid in the form of normal saline or lactated ringers solution. Colloid solutions such as albumin or hetastarch are usually reserved for those patients with ongoing bleeding to prevent a fall in oncotic pressure. Dextran may affect platelet function and should be avoided. Based on clinical evaluation of tachycardia, blood pressure and capillary refill, more such fluid boluses should be given.

Overexpansion of intravascular volume is potentially dangerous, particularly in bleeding varices but also in bleeding gastric or duodenal ulcers. Therefore, following correction of shock, further intravenous volume replacement should be titrated to match continuing blood loss. The decision to begin a transfusion is dependent on the initial hematocrit, and evidence of ongoing bleeding. In a patient who has stopped bleeding, a blood transfusion is given to restore the hematocrit to approximately 30 percent and allow some reserve in case of rebleeding. In this case, packed red blood cells (10 ml/kg initially) are recommended to reduce volume load. In the patient with continuous bleeding, ongoing blood transfusion is the only means of maintaining adequate oxygen carrying capacity. In this case the rate of transfusion is determined by the rate of bleeding. The use of packed red cells, filters and blood warmers minimize some of the risks involved with massive transfusion. Group O-negative packed cells can be used until type-specific blood is available. Hypercitratemia, hyperlactic acidemia hypocalcemia, thrombo-cytopenia and decreased clotting factors are associated with massive transfusions.[14] The patient should be given intravenous calcium and fresh frozen plasma after every 40 to 50 ml/kg of packed cells to prevent these complications. In addition platelet levels should be monitored and platelets given as needed.

In patients with initial signs and symptoms suggestive of 20 to 25 percent blood loss, oxygen should be administered via a face mask or nasal canula. In addition invasive monitoring should be considered to facilitate fluid management as mentioned previously. This includes an intra-arterial line to monitor blood pressure and oxygen saturation, and a central venous catheter to monitor central venous pressure. Inotropic support may be required after CVP has been restored to 8 to 10 cm H_2O. Depending upon the etiology of GI bleeding, if the patient has hepatic failure and impaired coagulation and ARDS, mechanical ventilation with optimum PEEP may be required to maintain adequate oxygenation.

Therapeutic Modalities

Whatever the cause of bleeding the specific goal is to provide therapy, either symptomatic or directly aimed at the bleeding site. Traditionally, iced saline lavage via a nasogastric tube was utilized in an effort to stop upper GI bleeding. Not only is its efficacy unproven but recent studies have identified several adverse effects. Cooling in animals results in a prolonged prothrombin and bleeding time, as well as reduced tissue oxygenation due to a shift in the Hemoglobin-oxygen dissociation curve to the left (hemoglobin binds more tightly to oxygen). This together with cold induced vasoconstriction of gastric vessels may predispose the gastric mucosa to stress ulceration. Finally hypothermia with resultant cardiac conduction and metabolic derangements may occur in younger patients. It is recommended then that iced-saline be abandoned in favour of saline or tap water at room temperature for the express purpose of diagnosis and clot removal.[15-17]

Intravascular infusion of vasoactive agents has been well described. Vasopressin has been the agent of choice. Continuous intravenous infusion is just as effective as intra-arterial.[18] The initial dose is 0.2 unit per 1.73 square meter per minute, but may be increased to 0.4 unit per minute if no response. Vasopressin has been especially useful in prehepatic portal hypertension, Mallory Weiss tear, and stress induced gastritis. Close monitoring is necessary to avoid arrhythmias, hypertension, oliguria and seizures due to water retention. Somatostatin has recently been advocated for upper GI hemorrhage owing to its action in reducing gastric blood flow, and inhibiting gastric acid and gastrin production. No studies in children have been reported, but in adults somatostatin has been found to be as effective as vasopressin with fewer complications in cirrhotic patients with, variceal hemorrhage.[19]

Most children with acute hemorrhage secondary to peptic ulcer disease or a mucosal lesion will stop bleeding with any therapy that raises gastric pH to greater than 5. Antacids have been the historical standard and are given at a dose of 0.5 ml/kg (maximum 60 ml/dose) every 1-2 hours. If a nasogastric tube is in place, the dose can be titrated to keep the gastric pH at 5. Use of a product with both magnesium hydroxide and aluminium hydroxide decreases the diarrhea seen with magnesium hydroxide. Although the H_2 receptor antagonists offer more convenience in administration, no study to date has shown them to be superior to antacids in the treatment of acute gastrointestinal bleeding, or in the prevention of stress ulceration.[20-22] Sucralfate has been reported to be just as effective as either H_2 receptor antagonists or antacids in the prevention of stress ulceration.[23] In addition, omeprazole has recently been reported to be effective. In refractory chronic esophagitis in infants and children, but its role in the treatment of acute upper GI bleeding in children has not been studied.[24]

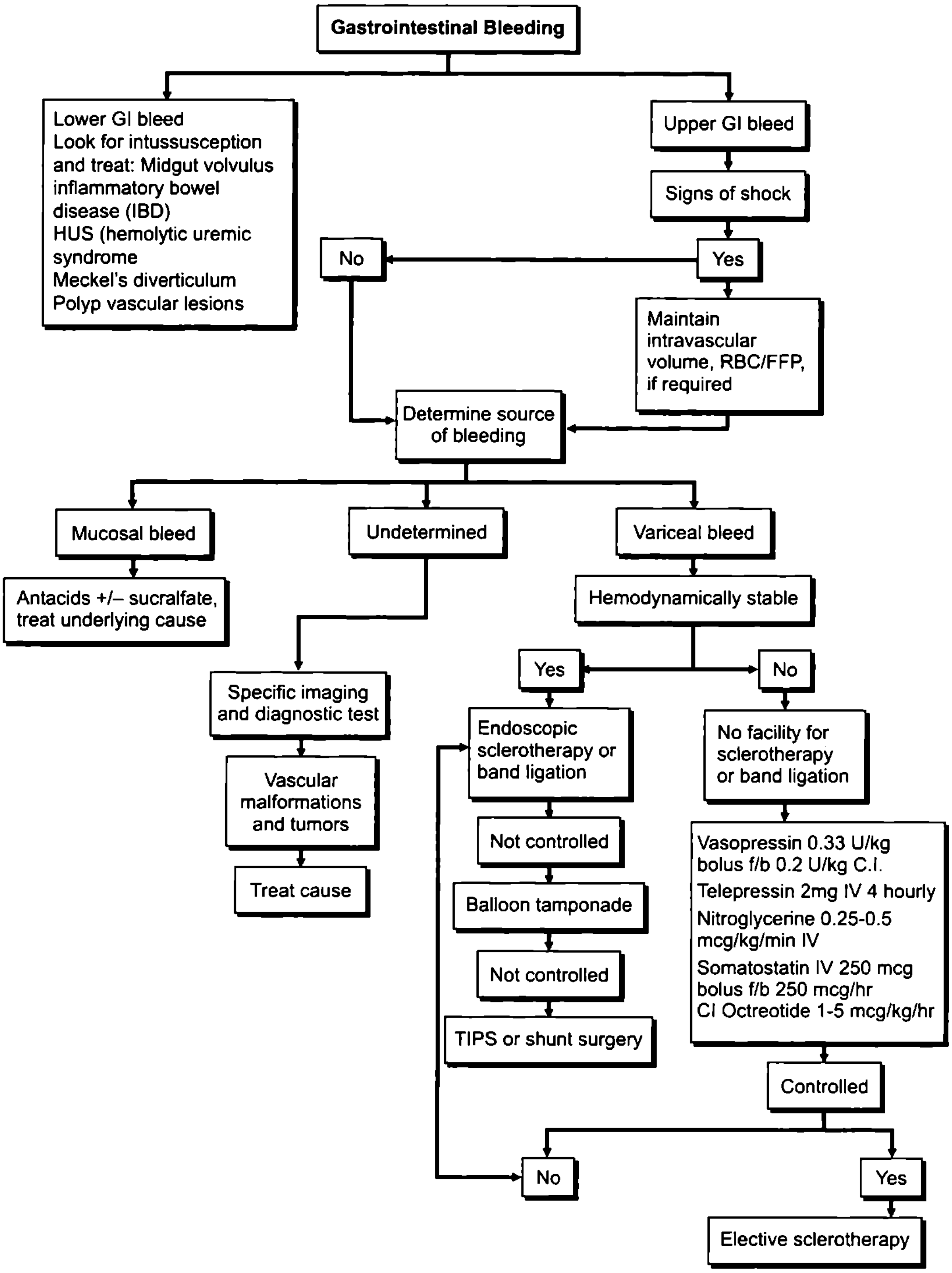
Treatment of bleeding esophageal varices has included vasopressin, as mentioned above, balloon tamponade, and sclerotherapy. The Sengstaken and Blakemore tube for temponade has been a mainstay in therapy since the initial report in 1950. Although this tube is now available in a pediatric size and can temporarily arrest hemorrhage, its use may be associated with serious complications including esophageal rupture, pulmonary aspiration, and airway obstruction.[25] Indications include massive life threatening hemorrhage or continued bleeding despite 2 to 6 hours of intravenous vasopressin. Insertion should only be by a physician skilled in its use. A detailed description of its usage in children has been described.[25]

Sclerotherapy involves the injection of a sclerosing agent directly into the esophageal varix, or into para-variceal tissue. Experience in children is accumulating and studies have demonstrated effective control of acute bleeding and decreased recurrent episodes.[26] Side effects include esophageal ulceration, perforation, stricture formation, esophageal dysmotility, spinal cord paralysis, and distress. Unfortunately, rebleeding remains constant concern until sclerotherapy completely obliterates the varices. Obliteration of bleeding lesions, i.e. vascular malformations and bleeding peptic ulcers with sclerosing solutions has been reported but experience in children remains limited. Thermal coagulation with heater probe electrocoagulation and photocoagulation are techniques widely utilized in adults to control active bleeding but no series on the use of these instruments has been published to assess their efficacy and side effects in children.[27]

SUMMARY

Gastrointestinal (GI) bleeding (Flow chart 67.1) in infants and children provokes alarm in parents and often anxiety in pediatricians. While this clinical situation has not changed over the years, advances in endoscopy and radiology as well as new therapeutic modalities allow more accurate identification of the site of bleeding. Although the majority of GI bleeding in the pediatric population is self limiting, a systematic approach including prompt assessment diagnosis and treatment is necessary to preclude undue morbidity. Emergency therapy of massive upper or lower gastrointestinal bleeding is directed at prompt initiation of fluid resuscitation and transfer to the pediatric ICU for further monitoring, blood transfusion and efforts directed at control of bleeding. Patients with hepatitis or varices deteriorating to massive bleeding and disseminated intravascular coagulation may present as ARDS (Acute respiratory distress syndrome) requiring mechanical ventilation and treatment in the PICU.

Flow chart 67.1: Gastrointestinal Bleeding


Gastrointestinal Bleeding
Lower GI bleed
Look for intussusception and treat: Midgut volvulus inflammatory bowel disease (IBD)
HUS (hemolytic uremic syndrome
Meckel's diverticulum
Polyp vascular lesions
Upper GI bleed
Signs of shock
No
Yes
Maintain intravascular volume, RBC/FFP, if required
Determine source of bleeding
Mucosal bleed
Undetermined
Variceal bleed
Antacids +/– sucralfate, treat underlying cause
Specific imaging and diagnostic test
Vascular malformations and tumors
Treat cause
Hemodynamically stable
Yes
No
Endoscopic sclerotherapy or band ligation
No facility for sclerotherapy or band ligation
Not controlled
Balloon tamponade
Not controlled
TIPS or shunt surgery
Vasopressin 0.33 U/kg bolus f/b 0.2 U/kg C.I.
Telepressin 2mg IV 4 hourly
Nitroglycerine 0.25-0.5 mcg/kg/min IV
Somatostatin IV 250 mcg bolus f/b 250 mcg/hr
CI Octreotide 1-5 mcg/kg/hr
Controlled
No
Yes
Elective sclerotherapy

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CHAPTER

68

Nutrition in the Pediatric Intensive Care Unit

Reeta Singh, Praveen Khilnani

Protein energy malnutrition is a common occurrence in Pediatric Intensive Care Units (PICUs) due to the response induced by critical illness, poor assessment of nutritional needs in critical illness, as well as lack of urgency/priority by the pediatrician or the intensivist being too involved with the drug therapy, hemodynamic support, and mechanical ventilation. It has been shown that severity of illness correlates well with alteration in energy metabolism in children.[1]

Starvation stress in critically ill children (with trauma, shock or infection) induces more stress response than simple starvation. It is associated with elevated serum catecholamines, aldosterone, antidiuretic hormone, glucocorticoids, insulin and glucagon.[2,3]

At the cellular level macrophages and polymorphonuclear leukocytes release various peptides like cytokines, interleukin-1 and tumor necrosis factor.[4-6] Despite elevated insulin levels, hyperglycemia and glucose intolerance are frequently observed because of counter regulatory hormones, primarily due to mobilization of alanine, glutamine and other amino acids from muscle and their biosynthesis to glucose and urea by the liver. There is insuppressible lipolysis and decreased ketogenesis. Most critically ill children are in negative nitrogen balance.[7-9]

The protein catabolism far exceeds protein synthesis. The net effect is rapid depletion of lean body mass termed as obligatory autocannibalism.

A comparison of simple starvation and stress hypermetabolism is shown (Table 68.1).

The difference in stress hypermetabolism includes proteolysis and increased urea nitrogen loss, less ketosis, and more gluconeogenesis. A stress factor (Fig. 68.1) needs to be added to modify nutritional therapy depending on severity of critical illness. For example, in major burns the resting metabolism may increase to 200 percent, 150-160 percent in septic peritonitis and nitrogen excretion is directly proportional. In addition, trauma and surgical stress are significant factors affecting nitrogen balance and outcome. It has been clearly shown that neonates can mount significant stress response similar to adults in response to surgical stress.[10,11]

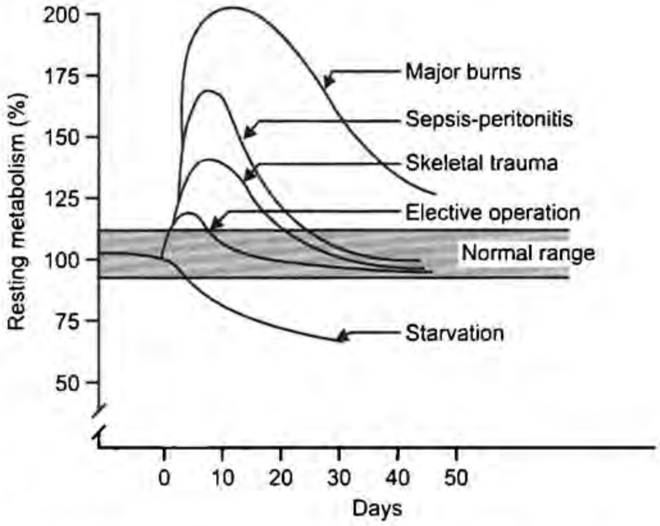

Fig. 68.1: Changes in resting energy expenditure over time as a function of level of stress

Table 68.1: Comparison of starvation and stress hypermetabolism

	Starvation	*Stress hypermetabolism*
Resting energy expenditure	Decreased	Increased
Respiratory quotient	Low (0.65)	High (0.85)
Mediator activation	–	+++
Regulatory responsiveness	++++	+
Primary fuels fat mixed proteolysis	+	+++
Branched chain	+	+++
Oxidation	–	–
Hepatic protein	+	+++
Synthesis	–	–
Ureagenesis	+	+++
Urinary nitrogen loss	+	+++
Gluconeogenesis	+	+++
Ketone body production	++++	+

MODES OF NUTRITIONAL REPLETION

Enteral, Parenteral or Both?

"When the Gut Works Use It'

It is a commonly expressed dictum, but pediatricians are often dissuaded by the difficulties involved in providing enteral nutrition, particularly in intensive care units, where it is easier to infuse nutrition through existing indwelling central lines, than deal with diarrhea, bloating and frequent interruptions in feeding. Even a small amount of enteral feeding appears to be effective in reducing mucosal atrophy, maintaining the enterohepatic enzyme system, and reducing the incidence of cholestatic jaundice.[12] Inotropic therapy is not a contraindication to institution of enteral feeds.

Additional minerals can be added without concern for solubility factors that hamper delivery in parenteral nutrition. This consideration is particularly important for calcium and phosphorus delivery for preterm infants, where requirements exceed parenteral solution solubility.[13,14] Enteral feeds reduce the incidence of intra abdominal and pulmonary sepsis after major trauma. Bolus feeds or continuous feeds may be administered as tolerated. Breast milk should be used as much as possible Commonly used enteral feed solutions include Lactogen, Pediasure (lactose based) other non-lactose based solutions (soy based). Isomil, Zerolac, Nursoy, Nusobee are also available. Pregestemil, Nutramigen, Peptamen are some of the simpler predigested elemental formulas. Details are available with manufacturers. TPN (Total Parenteral Nutrition) has been associated with an increase in septic morbidity, higher costs, and the induction of immunologic derangements which may magnify inflammatory response associated with injury and sepsis. Alverdy et al. showed in adult data that incidence of bacterial translocation is 66 percent with TPN in comparison with 33 percent incidence with enteral feeds.[15] However, with close monitoring of aseptic technique and metabolic status TPN can be safely administered in a critically ill child.

One way or the other nutrition must be started as soon as feasible after initial stabilization. In the pediatric ICU at authors institution, if feedings cannot be started by day 3 of admission to the PICU, or can-not be administered in adequate amounts, parenteral nutrition is begun to prevent negative nitrogen balance and to enhance lean body weight accretion. Enteral feeds should not be used in immediate postoperative period following gut surgery, peritonitis, pancreatitis, hemorrhage in the gut, necrotizing enterocolitis or short gut syndrome.

TPN can be used initially, and gradually when enteral feeds are begun, it can be tapered off. A judicious combination of enteral and parenteral nutrition should be used in the PICU.[16]

NUTRITIONAL ASSESSMENT

Groner and colleagues have demonstrated by indirect calorimetry, that children might have a different response to surgical stress than adults with respect to energy needs.[17]

Direct isotope studies to perform nutritional assessment are impractical. Indirect methods are commonly used to assess protein energy malnutrition such as anthropometric measurements including weight/height index, triceps and subscapular skin fold thickness (edematous states could result in falsely interpreted results).[18-24] Therefore proper history and clinical examination is most important in assessing nutritional status. Albumin, prealbumin, transferrin and retinol binding proteins levels are unreliable in sepsis, capillary leak syndrome and stress as an accurate index of nutrition, however in adult surgical patients, low albumin levels are associated with poor outcome. Total lymphocyte count, impaired cell mediated immunity has been correlated with nutritional status. Other indirect methods in use for assessment of nutritional status are as follows:

Basal Metabolic Rate (BMR)

Physiological differences between children and adults leave them at a significant nutritional disadvantage in times of stress. Nutritional stores are considerably less. Their basal metabolic rate (BMR) is higher and they need additional calories for growth. Furthermore, metabolic organs (brain, kidneys, liver and heart) make up a greater percentage of their body weight than adults. Energy requirements may be calculated approximately by multiplying the estimated BMR, as derived from the Harris Benedict equation, by a factor of 1.75.

Male BMR = $66 + (13.7 \times W) + (5.0 \times H) - (6.8 \times A)$
Female BMR = $65.5 + (9.6 \times W) + (1.7 \times H) - (4.7 \times A)$
where W = weight in kg, H = height in centimetres (cms)
A = age in years
BMR is calculated in units of kilocalories.

Catabolic Index

Catabolic Index = UUN – ($0.5 \times$ Nin + 3)
where UUN = 24 hr urine urea nitrogen in grams
Nin = 24 hr nitrogen intake in grams.

A catabolic index of < 0 indicates no significant stress; 0-5 moderate stress and > 5 indicates severe stress. Higher scores may predict which patient may benefit from aminoacid solutions augmented with branched chain amino acids. However, superiority of branched chain amino acid solutions when compared to other amino acid solutions is still controversial.

Stress factor is a simple method of estimating energy requirements in the hospital setting described by Souba and Wilmore.[22] The energy expended is calculated by multiplying the BMR with 1.25 and the stress factor for the particular illness. The stress factor in various illnesses is as shown in Table 68.2 and depicted as Figure 68.1.

Indirect calorimetery (Metabolic cart): Some western ICUs routinely use this method. In this method, the amount of oxygen absorbed across the lung is assumed to be equal to the amount of oxygen consumed in metabolic process. Energy expenditure could be measured to determine caloric needs:

Table 68.2: Stress factors in disease states

Condition	*Stress factor*
Mild starvation	0.85-1.00
Postoperative state	1.00-1.05
Cancer	1.10-1.45
Peritonitis and Sepsis	1.05-1.25
Multitrauma, burns	1.30-1.55

Energy expenditure = $3.586\ VO_2 + 1.443\ VCO_2 - 21.5$

CO_2 production is measured by measuring PCO_2 in expired gas. *Respiratory quotient (RQ)* is calculated as follows:

$$RQ = VCO_2 / VO_2$$

where $VCO_2 = CO_2$ produced, VO_2 = oxygen consumed
RQ is 1.0 for carbohydrates, 0.7 for fat, and 0.8 for proteins
RQ below 0.7 suggests fat as the main fuel, and >1.0 suggests lipogenesis.

Estimations of RQ are inaccurate if FiO_2 is >0.4. Further more, limitations in pediatric patients include leak in around uncuffed endotracheal tube. Use of metabolic cart in Indian settings is possible but impractical and should be reserved for particular patients where clinical estimates of energy requirements may be grossly inaccurate. About 30-40 percent of energy requirements should be composed of fat in infants and young children. Protein and fat requirements are listed in Table 68.3.

As a practical tip for the practitioner in the pediatric ICU, recommended caloric intake should not be based on tables but one should administer

Table 68.3: Protein and fat requirements in infants and children

	Age		*Protein (gm)*	*Fat (gm/kg)*
Infants	0-6	months	2.2 × kg	4-5
	7-12	months	2.0 × kg	4-5
Children	1-3	years	23	3-4
	4-6	years	30	3-4
	7-10	years	34	3-4
Males	11-14	years	45	2-3
	15-18	years	56	2-3
Females	11-14	years	46	2-3
	15-18	years	46	2-3

enough calories that it takes to achieve a clinical improvement with adequate weight gain (not due to fluid overload), normoglycemia and positive nitrogen balance as indicated by clinical examination (for muscle mass) as well as measurement of skinfold thickness to assess subcutaneous fat.

NUTRITIONAL SUPPORT

The need for energy to sustain growth and development make the pediatric patent different from an adult.

Carbohydrates

Goal of glucose is to provide energy and to spare lean body mass maximally without causing untoward side effects. Dextrose in concentration up to 12.5 percent can be used via peripheral intravenous line. Higher (usually 15 to 20%) concentrations require a central line for administration. This can increase the risk of fungal as well as bacterial infection if contamination of central line occurs.

Approximately 5-10 gram/kg/day (4-6 mg/kg/min) may be started, later modified (increase or decrease by 2.5-5 gram/kg/day) according to serum glucose levels and as indicated by weight gain and positive nitrogen balance. Glucose over administration does not increase oxidation or spare protein but may increase fever, CO_2 production, hepatic steatosis and smooth muscle breakdown. This in turn may result in respiratory, hepatic, gastrointestinal failure and delayed wound healing. In hypermetabolic state 25 kcal/kg/day may suffice to give permissive hypocaloric feeds in early resuscitative phase of critical illness.

Use of insulin with TPN has been shown to be of little benefit. Hyperglycemia may not be entirely due to glucose intolerance but due to increased gluconeogenesis that is unresponsive to exogenous calories. Nevertheless if high serum glucose > 250 mg/dl is causing osmotic diuresis, insulin may be added to the TPN.

Proteins

Children receiving TPN require approximately 1.5 to 2.5 g/kg/day of amino acids. Normal protein requirement in preterm infants is > 2.5 g/kg/day while at 4 to 5 months of age normal requirement is as low as 1.2 g/kg/day. In stress, protein requirement could increase by 200 to 300 percent in adults with pediatric studies showing similar results. Recommended energy to protein ratio is 84 kilo joules/gm of amino acid.[24-26]

Initial administration can be started with 0.5-1 g/kg/day to be increased by increments of 0.5 gm/kg/day. Locally available amnoacid solutions include Aminosyn, Aminosteril, Aminosteril Hepa (branch chain aminoacids), Celemin, Aminoplasmal, and Aminodrip. Details are available from product manufacturers.

Lipids

Small doses of soyabean or safflower oil (0.5 g/kg/day) prevents development of essential fatty acid deficiency. Proper use of lipids has nitrogen sparing effect. Above a minimal carbohydrate load lipid infusions and glucose have equal nitrogen sparing ability. Lipid therapy should be started with a dose of 0.5 gm/kg/day and titrated upwards at increments of 0.5 to 1 gm/kg/day to a final dose of 1-3 gm/kg/day.

Lipemia in serum and serum triglyceride levels are important indicators for decreasing/discontinuing lipid therapy temporarily. In septic patients, lipoprotein lipase activity is decreased, therefore, levels of serum free triglycerides and free fatty acids may be raised.

Fat microembolism may lead to decrease in pulmonary diffusing capacity, as well as increased venous admixture by elaboration of vasodilator prostaglandins that modify hypoxic pulmonary vasoconstriction. Lipids (long chain triglycerides LCT) can also depress leukocyte function and increase the levels of Prostaglandin E_2, an immunosuppressive agent. MCT (medium chain triglycerides), W-3 fatty acids and olive oil based emulsions are less immunosuppressive. Strict aseptic precautions need to be followed since contamination of lipid emulsions can cause fungal infections (Infection with malassezia furfur has been reported in neonatal ICUS). Commonly available lipid emulsions include Intralipid, Ivelip, lipolipid, celepid, and lipofundin (LCT/MCT) (all available as 10 and 20% emulsions). Details are available from manufacturers.

NUTRITION IN SPECIAL CIRCUMSTANCES

Nutrition in Liver Failure

The nutrition and dietary factors are implicated as important factors in pathophysiology and management of liver failure. The objective is to provide adequate protein and caloric support without worsening blood ammonia levels.[27] Diets containing vegetable proteins lower blood ammonia when compared with equinitrogenous diet containing animal proteins. Many studies have indicated association of clinical hepatic encephalopathy with decreased plasma concentration of branched chain amino acids: Isoleucine, leucine and valine and elevated levels of the aromatic amino acids: Phenyl alanine, tyrosine and tryptophan.[28] Despite that a precise combination of parenteral nutrition is not available in liver failure and serum ammonia, transaminases as well as clinical status needs to be closely monitored. The administration of poorly absorbed disaccharides as well as soluble fiber may have profound effects on nitrogen metabolism in the colon. Initially a low protein diet with parenteral dextrose should be used for patients in deep coma. Lactulose delivery via nasogastric tube should be commenced except in case of bowel obstruction. Stool pH should be kept below six. Lacitol (beta galactosido-sorbitol) is also effective.[29]

Nutritional Management of Acute Renal Failure[30,31]

Main aim is to minimize endogenous protein breakdown and to avoid fluid overload and electrolyte imbalance. In children with normal gastrointestinal tract enteral route is preferred.

Frequent small feeds are preferred over large feeds to prevent fluctuations in blood glucose levels. Carbohydrate intake should be approximately 3-5 gm/kg/day. Glucose polymers such as polycose, which contains 3.8 cal/ml can be added to the tube feedings. Protein intake is restricted to 0.5 gm/kg/day. Patients on dialysis require 1-2 gm of protein because of loss of nutrients in the dialysate. Increased amounts of glucose and essential amino acids may be put in dialysate.

Even with maximal supplementation, critically ill children with associated sepsis burns and other hypermetabolic states continue to breakdown endogenous protein because of hypercatabolism.[32,33] Various studies in carefully matched groups have shown considerably lower mortality in patients receiving glucose and amino acids than in patients receiving glucose alone.

Some of the commercially available intravenous amino acid mixtures contain acid salts which contribute to metabolic acidosis. In these cases acetate should be substituted for phosphates.

Some of the patients with low respiratory reserve may develop respiratory acidosis because of inability to eliminate excess CO_2 produced by large quantities of carbohydrates by increasing minute ventilation. In these cases, some of the carbohydrate intake should be substituted by fat calories in the form of medium chain triglycerides.

Nutritional Supplements

Vitamins

It is a common practice to use increased amounts of vitamins and minerals to compensate for loss during dialysis. Some of the recent reports have proved occurrence of secondary oxalosis in patients with renal failure and parenteral vitamin C administration suggesting limiting intake of vitamin C to 100 mg/day.[34] Vitamins must be provided to meet maintenance requirements as well as cater to losses and supervening stress. When provided intravenously, vitamins especially A, C, riboflavin and pyridoxine may be lost by adherence to plastic tubing and by photodegradation. Therefore, vitamins should be added to parenteral infusates shortly before administration and should be protected from light.[35]

Electrolytes and Minerals

The critically ill should be provided not only maintenance requirements of electrolytes but ongoing losses particularly from the gastrointestinal tract (GIT) need to be replenished. Phosphorus required due to accretion of calcium and phosphorus in the bone and to protein anabolism carry a requirement of 1.3 mmol/kg/day for every 400 mgm nitrogen/kg and 0.8 mmol calcium/kg. Magnesium requirements are usually met by 0.4 mmol/kg/day.[25]

Trace Elements (Table 68.4)

Trace elements are important component of all nutritional preparations, since deficiency can result in significant derangements affecting recovery from critical illness. Selenium deficiency is associated with abnormal polymorphonuclear and T-cell function due to role in antioxidant giutathione peroxidase.[36]

Zinc deficiency can result in diarrhea, mental depression, dermatitis, poor wound healing, platelet clumping and impaired chemotaxis.[37] Chromium deficiency is associated with glucose intolerance and peripheral neuropathy.[38]

Copper deficiency can cause hypochromic anemia, leukopenia and reduced levels of superoxide dismutase, a scavenger of superoxide free radicals.

Immunonutrition

Recently there has been increasing attention paid to modification in dietary components to affect the response to illness with the use of various immunonutrients including glutamine, arginine, omega 3 (ω-3) fatty acids and nucleic acids. Many studies have shown positive benefit in decreasing the rate of infection and length of hospital stay.[39, 40]

Glutamine

Glutamine is the major metabolic fuel for enterocytes and thus becomes important in maintaining the gut barrier. Glutamine is released from catabolized skeletal muscle in large amounts during stress and consumption by gastrointestinal tract is markedly increased. When added to parenteral nutrition, it improves nitrogen balance gut barrier function reduces infection and duration of mechanical ventilation.

Table 68.4: Requirements of trace elements in TPN

Element	Preterm µg/kd	Term µg/kd	Children µg/kd (Maximum/day)
Zinc	400	250< 3 mo 100> 3 mo	50(5000)
Copper	20	20	20(300)
Selenium	2	2	2(30)
Chromium	0.2	0.2	0.2(5)
Manganese	1	1	1(50)
Molybdenum	0.25	0.25	0.25(5.0)
Iodide	1	1	1(1.0)

(Source: CRNSS Delhi, 2001)

Ornithine Ketoglutarate

This produces glutamine through metabolic conversion, stimulates growth hormone secretion and in addition may correct underlying metabolic acidosis of trauma metabolism. Arginine and nucleotides have been supplemented with improved immune function.

Three hundred and twenty-six studies, using enteral feeds supplemented with immune enhancing nutrients such as arginine glutamine, nucleotides and omega 3 fatty acids, were analyzed by Heyland, et al. showing immunonutrition may decrease infectious complication rates but overall mortality was not improved.[41] Grimm, et al showed[42] that use of MCT (Medium chain triglycerides) and LCT (Long chain triglyceride), polyunsaturated omega 3 and 6 fatty acids (ratio 1 : 2), olive oil, and addition of arginine, glutamine, cysteine, and taurine can enhance immune response in critically ill patients. Levy J et al.[43] have reviewed in detail regarding Iron, zinc, selenium and vitamin A, arginine, glutamine and nucleotides and their immune-modulatory properties, probiotics (specific microbial feeds) and prebiotics (complex carbohydrates).

IMN impact (novartis), an enteral feed contains arginine, purine nucleotides and omega 3 fatty acids reduced morbidity but there was no change in mortality in critically ill in a randomized prospective study reported by Bihari et al.[39]

Prebiotics

Carbohydrates that enhance short chain fatty acid production and increase bacterial fermentation in the colon, and may alter bacterial flora in the small bowel and colon.[44]

Fiber and Probiotic Bacteria

Bacterial breakdown of fiber in the colon produces the short chain fatty acids which are substrates for colonic mucosa.[45]

Omega-3 Fatty Acids

Most enteral feeds contain omega-6 fatty acids. Preliminary studies show a trend to reduced infection in patients using fish oil (rich in Omega-3 fatty acids) as their fat source (Alexander JW).[46]

Immunonutrition has not been shown to affect out-comes in critical care, however evidence of reduction in infection rate is a significant one warranting its use if cost permits.

CONCLUSION

Malnutrition in the hospitalized patient is increasingly being recognized as an important factor determining outcome of the disease. There is growing evidence that early and appropriate goal-oriented nutritional support in the ill child aids recovery. Current nutritional management is based on a rapidly emerging knowledge of the special nutritional requirements related to the vastly different physiologic and metabolic characteristics of these patients. These children often present with significant metabolic derangements in protein and energy metabolism characterized by increased protein breakdown unsuppressed by protein or energy intake, reprioritization of protein synthesis with increased synthesis of acute phase proteins, decreased synthesis of structural proteins and increased turnover. In addition, there is also glucose and lipid intolerance.[47] Adequate nutritional and metabolic support of the critically ill child under these conditions is a daunting task. It involves an accurate calculation of caloric delivery with a precise mixture of carbohydrates, proteins, lipids and micronutrients which needs periodic review. The route of nutrient delivery also needs contemplation with increasing popularity of enteral feeding in this group. Emerging knowledge of the non-nutritional functions of nutrients has added another dimension to critical care and nutritional support.

Due to high incidence of malnutrition in hospitalized children with associated morbidity and mortality, it is imperative to institute early metabolic support in the critically ill child. Depending on the individual patients degree of malnutrition, gastrointestinal function, medical status and nutritional requirements either enteral (preferably if the gut works) or parenteral nutrition may be used to support the patient nutritionally with close monitoring for potential technical or metabolic complications. Whether or not this approach can alter outcomes in critically ill children needs to be evaluated by more scientific studies. But clearly, nutrition once thought to be only supportive has now proven to be thera-peutic in all adult, neonatal and pediatric intensive care units.

SUMMARY

1. Stress factor should be considered in critical illness for increased protein requirement.
2. Permissive hypocaloric feeds in early resuscitative phase (25 kcal/kg/day) and maintain normoglycemia.
3. Use the gut if it works via nasogastric, nasoduodenal or nasojejunal (NG/ND/or NJ) tubes.
4. TPN can be life-saving in NEC (necrotizing entero-colitis), peritonitis, short gut, bleeding from gastro-intestinal tract (Caution: Complications).
5. A judicious combination of enteral and parenteral nutrition can be used.
6. Breast milk should be used whenever feasible.
7. Immunonutrition may be tried if cost permits.
8. Do not forget trace elements.

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CHAPTER

Parenteral Nutrition for the Pediatrician

Pankaj Vohra

Parenteral nutrition (PN) has been in use for over 30 years in most parts of the world. It has proved to be life saving when used appropriately. However, the indications of PN are limited and enteral nutrition remains the first choice unless it is impossible, inadequate or dangerous to use. Hence, before starting PN one must ask the question—can the child be fed enterally?

PN is required if it is felt that the child will not be able to start enteral feeds within 5 days and it will be required for at least 4-5 days.

PN can be administered in 2 ways—via a central venous catheter or through a peripheral venous line (Table 69.1).

In practice, most children can be managed with PN through the peripheral line. However, some children will need a central line if PN is required for a prolonged period of time (at least 2 weeks) or there is a restriction of fluid that can be administered–hence requiring a high concentration of dextrose to deliver the required calories.

Contents of PN

1. *Carbohydrates* Usually dextrose is used though sorbitol and fructose have also been used. Carbohydrates provide bulk of the calories in PN.
2. *Protein* Crystalline amino acids are used. Protein is primarily meant for anabolism rather than being used as a fuel and hence adequate calories must be provided to spare the protein. It is estimated that 150 non-protein calories per gram of nitrogen (6.25 gram of amino acids) promotes anabolism. Certain amino acids are essential in newborns and young infants like histidine while proline, cystine and cysteine are considered as semi-essential. Phenylalanine, threonine and methionine are required in less amounts in young infants.
3. *Lipid* Long chain fatty acids or a combination of long chain fatty acids and medium chain fatty acids are used. A 20 percent solution is more useful than a 10 percent solution. This is because in the former, energy is more concentrated and

Table 69.1: Comparison of PN through central line versus peripheral line

Central line	*Peripheral line*
• Skill required to place and maintain	• Minimal skill required
• Can use 20 percent dextrose solution and hence useful if 800 mosm/l—limiting dextrose content to 10%	• Limit on osmolarity of the solution to fluid volume is restricted
• Total calories delivered higher	• Limit on the total calories delivered
• Infection rate and mechanical complications higher	• Infection rate and mechanical complications low but phlebitis very common

Table 69.2: Calorie content of different PN components

Dextrose	3.4 kcal/gram
10% Lipid	1.1 kcal/ml
20% Lipid	2 kcal/ml
Protein	4 kcal/gram

the concentration of phospholipids is less. Phospholipids inhibit the enzyme lipoprotein lipase. Lipids are hypo-osmolar and may be used through the peripheral line. Lipid preparation of combined long chain and medium chain fatty acids is a preferred product. Caloric contents of different PN components are shown in Table 69.2.

4. *Electrolytes* Sodium, potassium, calcium, magnesium and phosphate are required. There is no readily available preparation of phosphate available in India presently.
5. *Minerals* Trace elements viz. zinc, manganese, chromium, selenium, iodine, molybdenum and copper are usually required if long-term PN is being planned and is widely available.
6. *Vitamins* Fat and water-soluble vitamins are recommended for use. Usually a parenteral multivitamin is used.
7. *Water*

What to do Before Starting PN?

1. Ensure that enteral feeding is not feasible or is not enough.
2. Ensure that the child has a good intravenous access-peripheral or central.
3. Ensure that the electrolytes, blood sugar, triglyceride level, renal parameters and liver functions are normal or near normal. Abnormal values are not contraindications of PN but need more care and adjustments.
4. Calculate the fluid requirement of the child based on weight and the overall condition of the child.

Contraindications to PN

Contraindications to PN are few and include:

1. Enteral nutrition feasible
2. Enteral nutrition feasible within a few days
3. Severe dyselectrolytemia
4. Severe renal or liver derangement
5. Allergy to any of the components e.g. severe egg allergic individuals should not be administered lipid
6. Severe sepsis
7. Lipids should be excluded if there is extreme thrombocytopenia (Platelet < 5000/mm^3) or presence of bleeding in presence of thrombocytopenia.

Table 69.3: Suggested intake of calories in children in different age groups

Infants	100 kcal/kg/day
1-7 years	75-90 kcal/kg/day
7-12 years	60-75 kcal/kg/day
12-18 years	30-60 kcal/kg/day

Caloric Needs of a Child

Table 69.3 gives an approximate estimate of the caloric requirement of a child.

It is however, important to remember that critically ill children do not tolerate excess calories. Dextrose is not metabolized as in less critically ill children resulting in hyperglycemia, hyperinsulinemia and hepatic steatosis. Hyperglycemia results in glycosuria, increased carbon dioxide production (may be detrimental to children with respiratory distress or on the ventilator) and reduction of the neutrophil function. Hyperinsulinemia results in increased sodium and water retention and inhibition of lipolysis. Hence, the caloric requirement suggested for critically ill children is two-thirds of their requirement. This is so far only the first couple of days. This also allows PN to suffice for the initial 2-4 days till enteral feeds can be started to supplement the total calorie intake. Optimal blood sugars are less than 200 mg/dl.

How to Get Started?

Table 69.4 shows the standard doses of the different components of PN suggested for use on day 1.

Table 69.4: Initial requirement of different components of PN

Dextrose	4-6 mg/kg/min
Lipid	1 gm/kg/day
Amino acid	1 gm/kg/day
Sodium	2-3 mEq/kg/day
Potassium	2-3 mEq/kg/day
Calcium	0.5-1.0 mEq/kg/day
Magnesium	0.25-0.5 mEq/kg/day
Phosphate	1-2 mEq/kg/day

Hence, to actually write the PN, the following steps will help:

1. Calculate the total fluid requirement
2. Calculate the total calories recommended
3. Calculate the total calories and fluid taken up by lipids and amino acid component
4. Add the total fluid made up by amino acid and lipid components and subtract from the total fluid requirement. This will be made up by the dextrose and electrolyte containing fluid the concentration of which will then depend upon the total volume available.
5. Lipids should not provide more than 50 percent of the total calories being delivered. The usual calorie distribution is carbohydrate 50 percent, lipid 35-40 percent and protein 10-15 percent.

As mentioned earlier for positive nitrogen balance to occur, 150 non-protein calories have to be provided per gm of nitrogen. Hence, if the volume of lipid and amino acid is exceeding total fluid intake or not enough calories can be provided through dextrose, it may be wise to cut back on the amino acids and if necessary lipids. Amino acids used as fuel causes excess metabolic load (metabolic acidosis) and is undesirable.

How to Administer the PN?

The three major components of PN may be given separately or together. This would mean that in the former different components will mix at the time of delivery at the site of the intravenous line while in the latter all the components are mixed together in the bag. Many companies are now promoting their 'all in one bag' to make it convenient to administer through the peripheral line or central line. However, the smallest bag available currently is a 1-liter bag and hence may be useful for only the older children. These also contain calcium (and phosphate) and hence care must be taken to ensure the peripheral line is suitable for infusion to avoid extravasation and necrosis.

If the PN is given separately, it is advisable to run the dextrose containing fluid and the amino-acids continually over 24 hours while the lipid should be infused at a rate not exceeding 0.15 gm/kg/hour. Hence, lipids can be infused over 8-16 hours though if more convenient it can also be infused over a 24-hour period.

In general no test dose is required for the amino acids. However, it is advisable, to give a test dose for lipids even though allergies are very rare. The test dose is given as the follows: Infuse the lipid at the rate it has been planned for 15 minutes. Then stop the infusion for 15 minutes and watch for any evidence of allergy or anaphylaxis. If there are none then restart the infusion.

There is a lot of debate regarding use of 'filters'. At present due to the high cost and erratic supply, filters are not being used in many hospitals using PN.

Most centers do not recommend using heparin in the PN fluid. Heparin induces lipoprotein lipase enzyme and helps clear fat faster plus helps in keeping the central line patent. There is no role of heparin in peripheral PN.

If a central line is being used and a >10 percent dextrose solution is being administered it is advisable to increase the rate of the fluid infusion slowly. Hence if a 20 percent dextrose solution has been planned, run the infusion at half the desired rate for about 4 hours and at 75 percent of the desired rate for another 4 hours and then run at the full rate. This ensures that there is no hyperglycemia and glycosuria. However, if daily cycling of PN is planned for the child (usually for long-term PN), the infusion rate should run at half the infusion rate for 1 hour and when stopping, it should again run for 1 hour at half the rate to avoid hypoglycemia.

What to Monitor When a Child is on PN?

There are several things that need to be monitored daily and PN should be re-written daily.

1. Daily weight and input-output charting.
2. Initially, urine sugars (or blood sugars) need to be done 6 hourly to monitor for glycosuria and hence adjustments in dextrose concentration and/or infusion rates will have to be made. Once the child tolerates the PN, it is required to check sugar levels daily for the first week only. If a child is stable at a particular dextrose concentration, and starts to have hyperglycemia, consider the possibility of impending sepsis.
3. Electrolytes need to be checked daily till stabilization and then 2 times a week. For prolonged PN it may be checked once every week.

Table 69.5: Recommended increase in PN

Constituent	Increased by	Maximum
Amino acid	0.5-1 gm/kg/day	Infants 2.5 -3 gm/kg/day 1-13 years 1.5-2.0 gm/kg/d >13 years 1-1.5 gm/kg/day
Lipid	1 gm/kg/day	2.5-3 gm/kg/day

4. LFT (Liver function tests), RFT (Renal function tests), calcium and phosphorous need to be checked once a week.
5. If the patient is on long-term PN, levels of trace elements need to be also checked.

How to increase PN?

Table 69.5 shows how to increase the concentration of lipids and amino acids. This may require a decrease in total dextrose solution volume or increase the dextrose concentration keeping in mind that 10 percent solution should not be exceeded if a peripheral line is being used.

Lipid increase is dependant upon the triglyceride level. The triglyceride level should remain less than 150 mg/dl, 8 hours after the lipid infusion is stopped. If the level is higher it would suggest that the fats are not being metabolized fast enough and hence increasing lipid delivery will not be useful.

When to Consider Decreasing PN?

Once 50 percent of the enteral intake is achieved, it is acceptable to start decreasing the PN. There are several ways to do this. Some experts feel that all the constituents can be decreased (for dextrose the concentration and volume) and others feel that amino acids can be stopped first followed by a decrease in dextrose concentration and volume. As lipids provide a concentrated form of energy this may be the last to be stopped. However, this needs to be tailored for each child.

PN can be stopped when 75 percent or more of the calories and protein intake are being met through the enteral route.

What are the Complications of PN (Table 69.6)?

Complications of PN are metabolic, infectious or mechanical. The latter two are mostly related to central line placement. However, with the peripheral line, extravasation of fluid can occur and necrosis may result especially if calcium is added.

PN related cholestasis is unusual if PN is used for less than 2 weeks. Some recommended ways to avoid steatosis and cholestasis include:

1. Early enteral nutrition even if it is trophic feeds
2. Avoiding excessive calories
3. Cycling of PN
4. Ursodeoxycholic acid

Table 69.6: Complications of PN

Metabolic
Hyperglycemia
Hypernatremia
Hyponatremia
Hyperkalemia
Hypercalcemia
Hypocalcemia
Hypophosphatemia
Hypomagnesemia

Infectious (usually with central line)
Local infection
Central line infection
Bacteremia
Septicemia

Mechanical (usually with central line)
Extravasation and necrosis (peripheral line)
Air embolism
Thrombus
Pneumothorax
Arrhythmias
Cardiac perforation
Brachial plexus injury

Miscellaneous
Fatty liver
Hepatic cholestasis
Gut atrophy with increased risk of translocation of bacteria in absence of any enteral nutrition
Increased CO_2 production with excess CHO
Pulmonary dysfunction with excess lipid infusion
Re-feeding syndrome

Table 69.7: Commonly available PN products

Dextrose	5%, 10%, 20%, 50% solution
Amino acid	5%, 10% in 100, 250 and 500 ml bottles
Lipids (LCT or LCT:MCT)	10%, 20% in 100, 250 and 500 ml bottles
Trace elements	3, 4 or 7 trace element containing solution
Vitamins	Multivitamin parenteral preparations

5. Cholecystokinin analogue
6. Precaution against sepsis, early and aggressiv treatment of sepsis.

What Products are Available?

Table 69.7 provides some of the PN product available in the market. This list needs constan updating as companies often withdraw products an introduce new ones. It is useful to get acquainte with one or two of each of the following to eas management decisions.

CHAPTER

70

Fulminant Hepatic Failure

Neelam Mohan

Fulminant hepatic failure (FHF), a rare manifestation of the liver disease, constitutes a medical emergency and carries a high mortality without liver transplantation. It arises from loss of hepatic parenchyma that may result from any of a number of liver insults. Most cases of fulminant hepatic failure in children have no identifiable cause, which has prevented a focus on the mechanism by which hepatocytes are killed.

FHF is not merely a disease involving the liver, it represents a multiple organ dysfunction syndrome (MODS), which frequently involves the kidneys, lungs, bone marrow, the circulatory system, and (per definition) the brain. Furthermore, patients with FHF are susceptible to severe infections. Cerebral edema and Septicemia are the most frequent causes of death in FHF. Orthotopic liver transplantation is a substantial advance in the therapy of FHF. In recent years, our understanding of FHF has increased in many areas. More liver transplantation centers with specialized liver intensive care units are being established, new surgical techniques such as split liver and auxiliary liver grafts are underway and new treatment ideas including extracorporeal liver assist devices (ELAD) and hepatocyte transplantation may be beneficial in the future.

Definition

Acute liver failure (ALF) or fulminant hepatic failure was defined in 1970 by Trey and Davidson as a potentially reversible condition as a consequence of severe liver injury in which encephalopathy develops within eight weeks of the onset of first symptoms in the absence of pre-existing liver disease.[1] O'Grady et al[2] used the term hyper-acute liver failure for all patients who present with encephalopathy within 7 days of onset of jaundice, acute liver failure if encephalopathy develops within 8-28 days of onset of jaundice and sub-acute liver failure if encephalopathy develops within 29-72 days (5-12 weeks).

The International Association of Study of Liver Disease (IASL) accepts the definition of acute liver failure as onset of encephalopathy within 4 weeks of jaundice and subacute hepatic failure from 4 weeks to 6 months.[3]

The most popular diagnosis among pediatricians presently is that it is a rare multi- system disorder in which severe impairment of liver function (INR $\geq$ 1.5 with encephalopathy or INR $\geq$ 2 with or without encephalopathy) occurs in association with hepatocellular necrosis in a patient with no recognized underlying chronic liver disease.[4] There is a subtle difference from the acute liver failure in adults where hepatic encephalopathy is the cornerstone of diagnosis but in children especially in infancy not only it is very difficult to identify signs of early encephalopathy but also encephalopathy can be a very late presentation.

Etiology

The most frequently recognized causes of fulminant hepatic failure are viral hepatitis and hepatic injury due to therapeutic drugs or other hepatotoxic chemicals (Table 70.1).

Table 70.1: Causes of fulminant hepatic failure in children

Etiology	Disease	Frequency
Neonates		
Infections	Hep-B, Herpes viruses, echovirus, adenovirus	Frequent
Metabolic	Galactosemia, Tyrosinemia, Neonatal-hemochromatosis, Mitochondrial disease	Moderately frequent
Ischaemia	Congenital heart disease, Cardiac surgery Myocarditis, Severe asyphyxia, *Budd Chiari syndrome	Rare
Vascular	HV Thrombosis, Haemangiomia, Hemangioendotheliomia	Rare
Others	Congenital Leukemia, Neuroblastoma	Rare
Older Children		
Drugs	Paracetamol, Volproate, Isoniazid, Halothane Phenytoin, Tetracycline, etc	Mod-frequent
Infection	HAV, HBV, HEV, HCV, Herpes viruses, EBV, CMV, Sepsis, others	Frequent
Toxins	Amanita phalloides, Carbontetrachloride Phosphorus	Rare
Metabolic	Hereditary fructose intolerance, *Wilson's disease, Bile acid disorders, FAO defects	Rare
Autoimmune	Hepatitis (Esp. type 2 with liver, kidney microsomal antibodies in serum)	Rare
Ischemia	Congenital heart disease, cardiac surgery, myocarditis, severe asyphixia, Budd Chiari syndrome	
Others	Malignancy	Rare

Abbreviations: HV—Hepatic vein, HAV—Hepatitis A virus, HBV—Hepatitis B virus, HEV—Hepatitis E virus, HCV—Hepatitis C virus, EBV—Ebstein Barr virus, CMV—Cytomegalovirus, FAO—Fatty acid oxidation.

**Budd Chiari Syndrome* results from suprahepatic obstruction of the hepatic veins usually seen in association with blood dyscrasias (polycythemia vera, systemic lupus erythematosus, oral contraceptive use, malignant disease, and hepatic vein webs).

**Wilson's disease* is the inherited disorder of copper metabolism that results in FHF in the older child. The acute hepatic presentation of Wilson's disease is characterized by hepatic failure, acute hemolysis hyperuricaemia and often low alkaline phosphatase value.

In many cases, the etiology is indeterminate. The indeterminate group may include FHF due to hepatitis B virus mutants, hepatitis non-A, non-B and non-C or due to medications and toxins that are not tested for because they are thought to be insignificant. To date, there is no strong evidence of hepatitis C as a cause of FHF. The causes of FHF vary geographically. For example, in the United Kingdom, acetaminophen (paracetamol) is the primary cause of FHF, while in the United States, FHF is largely due to indeterminate causes. In India, the commonest causes of FHF in children are infective hepatitis (hep A, hep E or both) followed by hepatitis B infection.[5,6] A list of causes of fulminant hepatic failure in children as seen at Sir Ganga Ram Hospital, New Delhi, is shown in Table 70.2.

In infants and children, the causes of fulminant hepatic failure vary by age.

Additionally, FHF can result from acute decompensation in a patient with chronic liver disease. Mechanisms of acute decompensation are (a) Frequently: infection, peritonitis, gastrointestinal bleeding, hepatorenal syndrome, protein overload, inappropriate use of diuretics and (b) Less often: acute viral hepatitis, drug toxicity, liver infarction, hepatoma, portal vein thrombosis.

Pathogenesis of Fulminant Hepatic Failure

In recent years, an improved understanding of the mechanism leading to hepatocyte failure has emerged, though it's still limited. Although the initial stimulus for liver failure may differ for each etiology, some similarities exist with regard to the involvement of the cytokine network.[7] Activation of kupffer cell seem to play a pivotal role in this setting (Fig. 70.1) as an important site for release of cytokines and eicosanoids and for the uptake of scavengers. The most important mediators are interleukins IL-1, IL-6, TNF-α (tumor necrosis factor) and endotoxin. It is currently unclear whether manipulation of one system (i.e. prostaglandins) can favorably affect the evolution of the entire MODS picture.

Table 70.2: Etiology of FHF, of cases seen at Sir Ganga Ram Hospital, New Delhi (Jan 1999- Aug 2005)

Older Children(-n) = 73		*Infants (n) = 8*	
• Viral Hepatitis	– 37 (50.6%)	• Viral Hepatitis	– 3 (37.5%)
– Hep A*	– 24	– Hepatitis-B (Perinatal)	– 1
– Hep Bs	– 5	– Hepatitis E	– 1
– Hep E	– 3	– Active CMV infection (NASBA**–Positive)	– 1
– Hep A + Hep E	– 3		
– 0thers ((herpes, Dengue)	– 2	• Neonatal Hemachromatosis	– 1
• Wilson's	– 7	• Interrupted aortic arch	– 1
• Autoimmune	– 2	• Sepsis	– 1
• Drug Induced / Toxin	– 3	• Unknown	– 2
• Ischaemia	– 4		
• Sepsis	– 3		
• Falciparum Malaria	– 1		
• Histiocytosis	– 1		
• Enteric Fever•	– 1		
• Unknown/Idiopathic	– 9		
• Not Investigated	– 5		

*3 had ass G6PD deficiency , 1 had ass Dengue,
**NASBA: Nucleic Acid Sequence Based Amplification
•Rising Widal, Blood C/s Negative

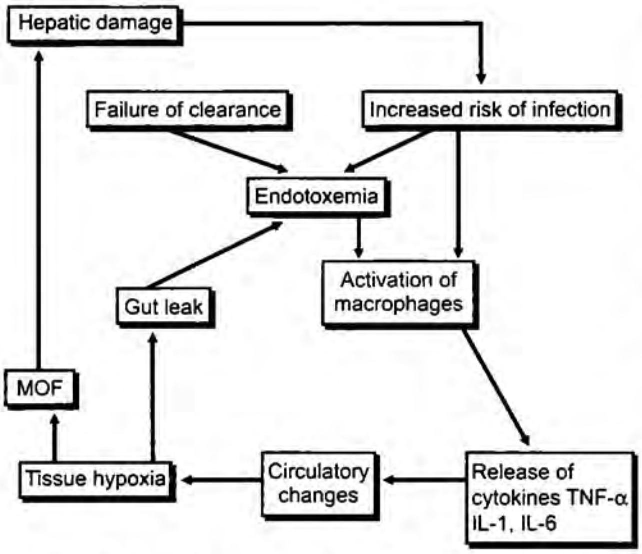

Hepatic damage
Failure of clearance
Increased risk of infection
Endotoxemia
Activation of macrophages
Gut leak
MOF
Tissue hypoxia
Circulatory changes
Release of cytokines TNF-α IL-1, IL-6

Fig. 70.1: Pathogenesis of fulminant hepatic failure

Encephalopathy is an important component of fulminant hepatic failure, and by definition it occurs in 100 percent of the patients. It results from indirect effect of hepatocyte failure on the function of brain. The neuropharmacological events that lead to clinical hepatic encephalopathy are complex and not yet completely understood. It is presumed that either the liver fails to produce appropriate amounts of neuro regulatory substances and/or fails to eliminate neurotoxins (ammonia) or depressants (1, 4 benzodiazepines), which result in brain dysfunction. Over the years many neurotransmitters or neurotoxins have been incriminated for causing or contributing to hepatic encephalopathy; these have included ammonia, glutamine, short chain fatty acids, aminoacids, mercaptans, octapamine and more recently gamma aminobutyric acid (GABA).

CLINICAL FEATURES

The clinical presentation varies with etiology but essentially there is hepatic dysfunction with hypoglycemia, coagulopathy and encephalopathy. A detailed CNS examination will identify various grades of encephalopathy (Table 70.3).

Table 70.3: Hepatic encephalopathy, classification of coma grades

Coma grade	*Characteristics*
I.	Slightly altered mental status, inverse sleep rhythm, Personality changes
II.	Confusion, drowsiness, asterixis
III.	Stupor, incoherence, sometimes agitated
IV.	Comatose, gradually more unresponsive, decerebrate posturing, seizures, ultimately areflexia.

Table 70.4: Warning signs of progressive diseases

- Grossly elevated aminotransferases
- A prolonged prothrombin time, which is unresponsive to vitamin K (particularly at presentation)
- Persistent jaundice with a rapid increase in bilirubin/ bilirubin >20 mg%
- Decreasing liver size along with decline in transminases and increase of bilirubin
- Increasing lethargy or occasionally hallucinations.
- Rarely hemorrhagic diathesis and systemic collapse.
- Hypoglycemia, Hypoalbuminaemia, Hyperenutation

Table 70.5: Investigations in fulminant hepatitis

Baseline Essential Investigations

Biochemistry

- Bilirubin, transaminases
- Alkaline phosphatase
- Albumin
- Urea and electrolytes
- Creatinine
- Calcium, phosphate
- Ammonia
- Acid-base, lactate
- Glucose

Hematology

- Full blood count, platelets
- PT (Prothrombin time), PTTK (Partial thromboplastin time), FDP (fibrin degradation products)
- +/- Factors V or VII, Reticulocyte count, G6PD (glucose 6 phosphate dehydrogenase, P/S (peripheral smear for MP (malarial parasite)
- Blood group, cross-match

Septic screen

- Omitting lumbar puncture

Radiology

- Chest X-ray
- Abdominal ultrasound
- +/– CT Scan or MRI

Neurophysiology

- EEG (electroencephalography)

Diagnostic Investigations

Serum

- Hepatitis A-IgM, Hepatitis E-IgM, HbsAg, Hepatitis B c IgM, HCV Antibody
- +/- Leptospira
- CMV, HSV, EBV
- Other viruses
- Paracetamol level
- Serum copper, Ceruloplasmin (> 3 years)
- Autoantibodies
- Amino acids

Urine

- Toxic metabolites
- Amino acids, Succinylacetone
- Organic acids
- Reducing sugar.

Jaundice may be a late feature, particularly in metabolic disease . The clinical onset may be within hours or weeks. FHF eventually represents a multiple organ dysfunction syndrome (MODS) involving the kidneys, lungs, bone marrow, circulatory system besides the brain. Therefore, the initial examination and biochemical investigations must establish hepatic, cerebral, cardiovascular, respiratory, renal and acid base status.

The signs that predict the development of FHF are depicted in Table 70.4.

Diagnosis

Diagnosis is established by a combination of clinical and biochemical features and specific diagnostic tests (Table 70.5). Biochemical features demonstrate marked conjugated hyperbilirubinemia, elevated aminotransferases raised plasma aminonia and coagulopathy. Liver histology is usually impossible to obtain because of the abnormal coagulation.

The common differential diagnosis includes viral hepatitis, drugs, toxins induced or metabolic liver disease.

Management (Flow chart 70.1)

The management of acute liver failure includes:

1. Assessment of prognosis for liver transplantation
2. Prevention of complications while awaiting hepatic regeneration or a donor liver
3. Hepatic support

Management should be in a pediatric intensive care unit. Priorities of intensive care management should include airway breathing and circulation. In patients with worsening encephalopathy (grade III, IV) and cerebral edema, increasing oxygen requirement, early acute respiratory distress syndrome (ARDS), or shock with or without multiorgan failure, endotracheal intubation and mechanical ventilation should be considered. Muscle relaxant of choice for endotracheal intubation is atracurium since it is metabolized by Hoffman non-enzymatic hydrolysis independent of liver or kidney disfunction. Norcuron should be avoided for muscle relaxation since it is matabolised by liver. Fentanyl or meperidine (pethidine) could be used for analgesia. A central venous catheter (femoral location is safest) will be required for assessment of central venous pressure and volume status. Use of a double lumen or preferably triple lumen catheter, which enables simultaneous administration of blood products, intravenous fluids and drugs is useful. An indwelling arterial line for measurement of blood pressure for biochemical and acid-base monitoring is essential. A nasogastric tube is put in with regular gentle saline lavage to detect upper gastrointestinal bleed. The urinary bladder is catheterized and strict output record maintained. Care should be taken for bed sores. Baseline biochemical and other investigations are performed (Table 70.6). Frequency of monitoring will depend on the severity of illness ranging from daily in mild cases to 4-6 hourly in patients with stage III and IV coma and include complete blood count, blood gases, electrolytes, aminotransferases and prothrombin time, plus daily monitoring of plasma creatinine, bilirubin and ammonia and chest X-ray to follow the ARDS and heart size. An abdominal ultrasound may indicate liver size and patency of hepatic and portal veins, particularly if liver transplantation is being considered. Maintenance fluid consists of 10 percent dextrose in 0.25 N saline and is usually restricted to 75 percent of maintenance. Vitamin K is given to all patients. The nursing of the patient should be in a quiet environment and avoid excessive stimulation and pain . Sedation should also be avoided. If the patient needs sedation he/she should be electively intubated for assisted ventilation.

The complications of acute liver failure are numerous and include: sepsis, gastrointestinal bleeding, cerebral edema, renal and cardiac failure. Gastro-intestinal bleeding is frequent and may be prevented by using H_2 antagonists and Sucralfate. Infection is a common complication of FHF, and a significant cause of death in these patients.[8] The role of broad spectrum antibiotics in the prevention of infection is controversial but there is growing evidence that the use of prophylactic antibiotics leads to a decrease in bacterial infections, fever deaths, and shortened hospital stay.[9] Catheterized patients receiving parenteral nutrition are at high risk of fungal superinfection and antifungal agents such as Fluconazole are particularly utilized pretransplant. The use of N-acetylcysteine, which is particularly useful in paracetamol poisoning, has anecdotal success in the management of acute liver failure.

Table 70.6: General Management (Flow chart 70.1)

- Nursing in a quiet environment
- Avoid excessive manipulation and pain
- Avoid sedation
- In patients with Grade III/IV encephalopathy and cerebral odema, consider elective intubation and ventilation
- Muscle relaxant of choice is atracurium. Avoid norcuron
- Fluid restriction to 2/3rd maintenance
- Strict input – output monitoring
- CVP monitoring and arterial BP monitoring preferably
- Prevention of hypoglycaemia – Use 10% Dextrose or more to manitol.
- Prevention of sepsis using broad spectrum antibiotics and antifungal agents.

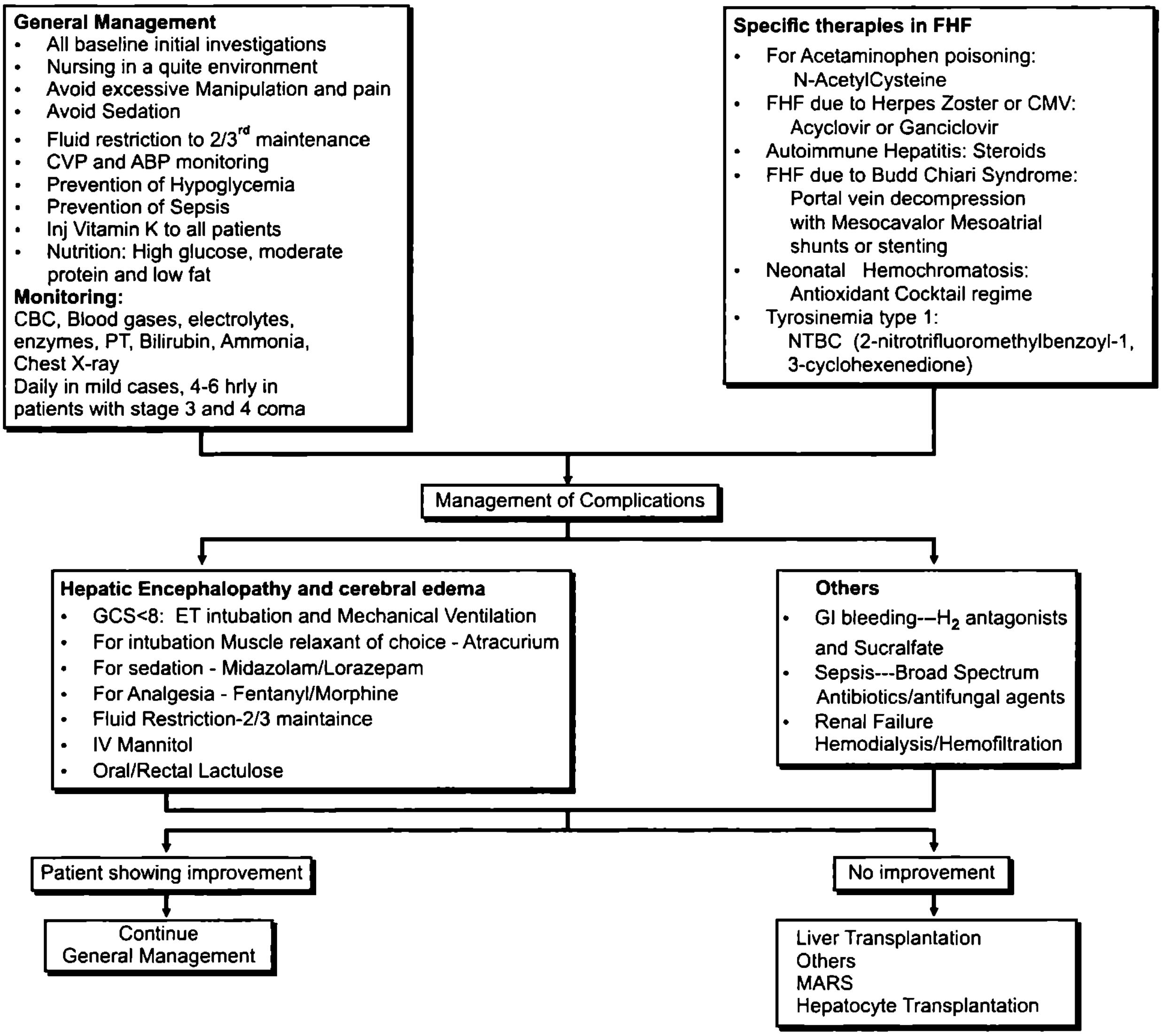
In the early stages of assessment prolongation of prothrombin time (PT) is a sensitive guide to prognosis and need for liver transplantation. If coagulation is severe (PT > 60 sec) and/or the decision for liver transplantation has been taken then coagulation support using fresh frozen plasma and cryoprecipitate and Vitamin K is essential. Exchange plasmapheresis rapidly and effectively corrects severe coagulopathy.

Metabolic, respiratory and renal complications needs to be tackled as and when necessary. Renal failure develops in 10-15% in Pediatrics ALF.[10] Renal failure is usually secondary to hepatorenal syndrome, occasionally due to acute tubular necrosis or drug toxicity (avoid aminoglycosides and contrast dyes). Hemodialysis or hemofiltration is indicated in severe metabolic acidosis, hyperkalemia and fluid overload. Hepatic renal syndrome can be reversed by liver transplantation.

Hepatic Encephalopathy and Cerebral Edema

Hepatic encephalopathy and cerebral edema represent two different neurological complications of acute liver failure. Although both conditions can present with similar symptoms-altered mental status and decorticate and decerebrate posturing–they each have different natural histories and management goals. Careful observation is necessary to detect the onset and progression of hepatic encephalopathy. Hypoxemia, hypoglycemia, sepsis, hypokalemia, and gastrointestinal bleeding exacerbate hepatic encephalopathy (Table 70.7) and should be identified and

Flow chart 70.1: Management of fulminant hepatic failure (FHF)



General Management
• All baseline initial investigations
• Nursing in a quite environment
• Avoid excessive Manipulation and pain
• Avoid Sedation
• Fluid restriction to 2/3rd maintenance
• CVP and ABP monitoring
• Prevention of Hypoglycemia
• Prevention of Sepsis
• Inj Vitamin K to all patients
• Nutrition: High glucose, moderate protein and low fat
Monitoring:
CBC, Blood gases, electrolytes, enzymes, PT, Bilirubin, Ammonia, Chest X-ray
Daily in mild cases, 4-6 hrly in patients with stage 3 and 4 coma
Specific therapies in FHF
• For Acetaminophen poisoning: N-AcetylCysteine
• FHF due to Herpes Zoster or CMV: Acyclovir or Ganciclovir
• Autoimmune Hepatitis: Steroids
• FHF due to Budd Chiari Syndrome: Portal vein decompression with Mesocavalor Mesoatrial shunts or stenting
• Neonatal Hemochromatosis: Antioxidant Cocktail regime
• Tyrosinemia type 1: NTBC (2-nitrotrifluoromethylbenzoyl-1, 3-cyclohexenedione)
Management of Complications
Hepatic Encephalopathy and cerebral edema
• GCS<8: ET intubation and Mechanical Ventilation
• For intubation Muscle relaxant of choice - Atracurium
• For sedation - Midazolam/Lorazepam
• For Analgesia - Fentanyl/Morphine
• Fluid Restriction-2/3 maintaince
• IV Mannitol
• Oral/Rectal Lactulose
Others
• GI bleeding--H2 antagonists and Sucralfate
• Sepsis---Broad Spectrum Antibiotics/antifungal agents
• Renal Failure Hemodialysis/Hemofiltration
Patient showing improvement
Continue General Management
No improvement
Liver Transplantation
Others
MARS
Hepatocyte Transplantation

Table 70.7: Encephalopathy – Aggravating factors

- GI hemorrhage
- Hypovolemia
- Potassium depletion
- Hypoglycemia
- Uremia
- Infections
- Constipation
- Sedatives and anesthetics
- High protein intake.

treated. A trial of oral or rectal lactulose can help reduce high levels of ammonia, although these medications are not as effective in FHF as they are in treatment of hepatic encephalopathy associated with chronic liver disease. Lactulose is administered in a dose of 1 ml/kg body weight via NG tube 3 to 6 times per day, to maintain loose, acid stool and regular stool output. Neomycin may also be helpful, in a dose of 125 to 500 mg, 4 times per day via NG tube.

More than 75-80 percent of patients, especially in stage 4 hepatic encephalopathy develop cerebral edema.[11,12] It is the most frequent cause of death in patients with FHF. Traditional signs of increased intracranial pressure (ICP) such as hypertension, bradycardia, increased muscle tone leading to decorticate rigidity and posturing, abnormal papillary reflexes and brainstem respiratory patterns, are unreliable in FHF.[13] Head CT is also an unreliable way to diagnose and follow ICP in FHF. However, it is indicated to exclude structural lesions including intracranial hemorrhage, as well as for ICP monitor placement.[14] Intracranial pressure monitoring in ALF is still an ongoing debate. Aim of ICP is to maintain ICP below 21 - 25 mm Hg and cerebral perfusion pressure (mean arterial pressure - ICP) at >50 mm Hg but it has not shown to affect the final outcome.

Fluid restriction (50% to 2/3rd maintenance) and the use of intravenous mannitol (0.5 g/kg over 4-6 hours) may be helpful in the short term. Serum osmolarity should not exceed 320 mOsm/l during mannitol therapy. As mentioned previously mechanical ventilation should be initiated if cerebral edema is suspected. Intubation must be carried out using a short acting muscle relaxants such as atracurium and sedation may be carried out with short acting benzodiazepines like midazolam and lorazepam. Fentanyl or morphine should be reserved for treating pain.

Convulsions should be promptly treated with phenytoin or phenobarbitone or thiopentone infusion.

Recent reports suggest that induction and maintenance of hypernatremia (145 – 155 mEq/l) by administration of 30% hypertonic saline can reduce the incidence and severity of intracranial hypertension in patients presenting with ALF[15] but a larger study will be required to prove its role as a prophylactic measure. Hypothermia (core body temperature of 32°C) has been shown to be effective in the management of severe intracranial hypertension with lowering of ICP and improvement of cerebral perfusion pressure in adults[16] but there are no studies regarding the use of hypothermia or maintenance of hypernatremia in children with ALF.

Specific Therapies in FHF

Specific therapies are only available for a limited number of causes of FHF. In FHF secondary to acetaminophen poisoning, oral N-acetylcysteine is administered in order to restore the glutathione stores. Recent evidence suggests that there may be advantages in starting N-acetylcysteine beyond 15 hours following ingestion of acetaminophen, and even as late as 36 hours following the event.[17,18] FHF due to Herpes zoster or CMV may be treated with acyclovir or ganciclovir. Patients with FHF due to the Budd Chiari syndrome may benefit from portal vein decompression with mesocaval or mesoatrial shunts or stenting. Patients with FHF from autoimmune hepatitis may benefit from a trial of steroids. Amanita Phalloides hepatotoxicity may benefit from the administration of silibinin, which is a flavinoid-alcohol, or penicillin G, which interferes with the uptake of alpha-amanitin into hepatocytes. This is useful up to 48 hours after ingestion of the toxin.[19]

Other therapies suggested for FHF have included steroids, which have no effect on mortality or cerebral edema, and may further compromise the immune system,[20,21] and prostaglandins, whose initial benefit[22] in the treatment of viral induced FHF has not been borne out in subsequent prospective randomized controlled trials.[23]

For neonatal hemochromatosis management includes anti-oxidant cocktail regime (N acetylcysteine-140 mg/kg, selenium (2-3 mgm/kg/day), alpha tocopherol polyethylene glycol succinate (20-30 IU/kg/day). Prostaglandin E1, (0.4-0.6 μgm/kg/hour) Desferrioxamine(30 mg/kg/day). Response is variable and it is more effective if begun within 24-48 hours of birth and in infants with a less severe phenotype. Liver transplantation is the definitive treatment for children who do not respond to medical therapy.[24]

Management of tyrosinemia type I an autosomally recessive disorder due to a defect in the metabolism of tyrosine, resulting in acute liver failure in infants between 1 and 6 months of age, has been transformed by treatment with NTBC (2-nitrotrifluoromethylbenzoyl-1, 3-cyclo-hexenedione) which prevents the formation of toxic metabolites and restores hepatic function.[25] Liver transplantation is now only required for those children who fail to respond to NTBC.

Hepatic Support in FHF

Recent research in hepatic failure has focused on the concept of hepatic support. Initial trial with techniques such as human cross-circulation, plasma exchange,[26] plasmapheresis, and charcoal hemoperfusion[27] have shown no significant survival benefit.

The most recent development of the Extracorporeal Liver Assist Device (ELAD)[28,29] or Bioartificial Liver (BAL),[30] is similar in technique to hemodialysis and uses liver cell lines placed in hollow perusable cartridges. Despite improvements in biochemical and clinical parameters, a recent trial failed to show an improvement in the clinical outcome.[31] Both direct hepatocyte transplantation,[32,33] and the use of hepatic growth factors are promising approaches to hepatic support in FHF, but have yet to be developed sufficiently before they are applied clinically. Recent advances include the application of MARS (Molecular Adsorbent Recirculating System) in patients of hepatic failure. MARS system is an extracorporeal non-biological liver support method based on the principle of dialysis, filtration and adsorption, that is its a combination of both kidney and liver dialysis. MARS uses human albumin to cleanse the blood because it can attract toxin bound to albumin in the blood that the aqueous solution in kidney dialyses cannot remove. The system replaces the detoxification function of the liver and preliminary results have been promising. Use of MARS in ALF in adults has been associated with hemodynamic stabilization, improvement in mental status and hepatic encephalopathy.[34] A recent metaanalysis, considering all forms of devises together demonstrated no efficacy for bioartificial liver devise for treatment of ALF.[35]

Orthotopic Liver Transplantation in FHF

Liver transplantation is the only proven therapy of FHF. Selection for liver transplantation depends on the etiology of the disease, prognostic factors,[36] presence or absence of multi-system disease and/or reversible brain damage. Perhaps the most frequently used criteria are those proposed by the King's College Group[37] (Table 70.8).

Table 70.8: Kings college criteria for liver transplantation in fulminant hepatic failure

A. For acetaminophen poisoning
- Arterial pH < 7.3
- Or the following 3 factors
  - Prothrombin time(PT) >100 sec
  - Creatinine > 3.5 mg%
  - Grade III or IV encephalopathy

B. For other causes
- P.T > 100 sec
- Or any 3 of the following
  - PT > 50 sec
  - Bilirubin > 17.5 mg%
  - Age < 10 years
- Cryptogenic or drug induced
- Jaundice for more than 7 days before onset of encephalopathy

Before considering a patient for liver transplantation, it is important to exclude multisystem disease and to diagnose a mitochondrial disorder (plasma and CSF lactate, muscle biopsy) or erythrophagocytosis (bone marrow aspirate). In neonates and infants, it is less easy to demonstrate irreversible cerebral damage because the cerebral sutures would not have fused and the classical signs of cerebral edema may not be present. The best guide to irreversible cerebral damage is the development of gray/white reversion on CT scan secondary to cerebral ischemia or the development of convulsions.

Liver transplantation could be:

1. Cadaveric
   a. Whole graft-when the whole liver is used.
   b. Split graft–when the donor liver is used for recipients.
   c. Reduced graft–when the donor liver is reduced to suit the size for recipient.
2. Living related–when a live donor gives part of his/her liver to the recipient.

For liver transplantation, blood group compatibility between the donor and recipient is a must. Cadaveric transplants are very popular in the west while in countries like Japan, mostly living related liver transplantation are undertaken. In India, there is tremendous lack of awareness regarding cadaveric donation. Mostly living related liver transplants have been carried. By the end of 2006, > 250 liver transplants have been carried in the country with the largest experience at Sir Ganga Ram Hospital where >110 liver transplants have been carried out. At the author's unit at Sir Ganga Ram Hospital 11 pediatric liver transplants have been carried out with a mean age 6.09 yr (1-13 yr). All patient are surviving, mean follow up of 14. 18 months (1 – 40 months). 2 of these transplants were in children with acute liver failure, one with underlying Wilson's disease and the other with hepatitis A. Both are doing well post transplantation.

Survival post liver transplantation for acute liver failure has improved and most recipients can expect a more than 70 percent, 5 year survival.

Auxiliary Orthotopic Liver Transplantation (APOLT)

Auxiliary Liver Transplantation: Auxiliary liver transplantation is when the liver graft is placed in the right upper quadrant beside the native liver. If the native liver recovers function, immunosuppression can be withdrawn and the heterotopic graft will undergo rejection and atrophy. In experience from hepatic Unit of King's college, London of the 16 children who received APOLT, overall survival was 87%, six of whom have shown evidence of liver regeneration. Of these six, immunosuppression has been stopped successfully in four and the other two are on tapering doses.[38] APOLT provides the option to discontinue what would have otherwise been the need for life – long immunosuppression and for this reason would be the transplant procedure of choice for most patients. However, this is not suitable for transplantation for ALF secondary to metabolic liver disease, as these livers are unlikely to recover and there may be a risk of hepatoma in the cirrhotic liver.

Hepatocyte Transplantation

Hepatocyte transplantation has been tried in experimental animals with improved survival. In a small number of clinical studies, variable improvement in encephalopathy, coagulopathy, and hyperammonemia has been reported. It may serve as a bridge to transplant but remains experimental still.

SUMMARY

Acute liver failure in childhood is a rare but fatal disease, which may develop secondary to infection, drugs, or metabolic liver disease. Biochemical features demonstrate marked conjugated hyperbilirubinemia, elevated aminotransferases, raised plasma ammonia and coagulopathy. Management is directed towards hepatic support, prevention and treatment of complications, and early consideration for liver transplantation. Earlier referral to specialized medical centers, prevention of hepatitis through vaccines greater supplies of donor organ and improved hepatic support systems will all lead to better outcomes. Innovative modalities to treat the complications of FHF may be the most important factors to improve the morbidity and mortality of this serious disease.

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CHAPTER 71

Liver Transplantation

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Orthotopic liver transplantation while experimental two decades ago has become a well-established procedure, which is considered now standard of care for the treatment of liver failure. The combination of new methods of immunosuppression and developments in both surgical transplant and microvascular surgical techniques has achieved survival rates in pediatric patients of 80-90 percent.[1-4] The first successful procedure in a child was performed in 1967.[5] With the introduction of combination immunosuppression comprised of steroids and cyclo-sporine in 1978, survival increased from 30-50 percent to on average 80 percent. Ongoing developments in microsurgical vascular techniques, the introduction of University of Wisconsin preservation solution, successful multiorgan harvest techniques, and improved experience with reduced size allografts have further prolonged survival rates and moreover increased the number of grafts available for allocation.

INDICATIONS

Liver transplantation is usually performed in patients with progressive liver disease with the expectation of liver failure, stable liver disease with known outcome of significant morbidity or mortality, hepatic based metabolic disease, fulminant hepatic failure, or primary localized malignancy. The timing of operation is based on clinical criteria: Intractable cholestasis, ascites, portal hypertension with variceal bleeding, repeated cholangitis, impaired synthetic function, encephalopathy or failure to thrive. In metabolic disorders, timing is planned to avoid complications or declining function (Table 71.1).

Table 71.1: Indications for pediatric liver transplantation

Cholestatic liver disease
- Biliary atresia
- Alagille's syndrome
- Scrlerosing cholangitis
- Familial cholestasis syndromes

Fulminant hepatic failure
- Viruses (Hepatitis A, B, C)
- Toxins
- Metabolic (Wilson's disease)
- Drugs

Metabolic disorders
- Antitrypsin deficiency
- Tyrosinemia
- Urea cycle defects
- Familial hypercholesterolemia
- Selected lipid storage disorders
- Selected glycogen storage disorders
- Neonatal iron storage disorders
- Crigler-Najar
- Hyperoxaluria type 1
- Hematologic disorders (hemophilia, porpheria)
- Selected organic acidurias

Chronic active hepatitis or cirrhosis
- Autoimmune
- Neonatal hepatitis
- TPN associated cirrhosis
- Cryptogenic cirrhosis

Neoplasia
- Hepatoblastoma
- Sarcomas
- Hepatocellular carcinoma
- Hemangioendothelioma
- Miscellaneous
- Budd-Chiari's syndrome
- Cystic fibrosis
- Caroli's disease

Biliary atresia is the most common indication for liver transplant in children. Mortality before 1959 was 100 percent. In 1959 Kasai developed a surgical correction with portoenterostomy.[6] Successful bile flow can be achieved in 40-60 percent of patients currently. However, over time upto 75 percent will require transplant for intractable cholestasis with portal hypertension and impaired liver function. In cases where a cause for failure has been identified, most patients had recurrent bouts of cholangitis. There is 90 percent mortality within five years without definitive repair of biliary drainage. Reattempts at biliary drainage for a failed portoenterostomy are generally unsuccessful.[7,8] In two patient series the first in 1984 out of Pittsburgh, and later at UCLA, survival in patients treated with transplant following a failed Kasai reported survival rates of 84 percent at two and three years and 78 percent at 5 years.[9,10]

Hepatic failure can be classified as fulminant or chronic. Fulminant hepatic failure is defined, as the development of liver failure with coagulopathy and encephalopathy within 8 weeks of the onset of symptoms in whom there was no history of liver disease. Further, onset may be acute (less than two weeks) or subacute (two to eight weeks). Most commonly fulminant hepatic failure follows viral hepatitis or drug toxicity. Less commonly it may be the result of toxins, autoimmune hepatitis or genetic/metabolic disease. Survival rates without transplant depend on the underlying etiology and clinical severity, but vary from 10-70 percent.[11,12] Poor prognostic factors include cerebral edema, acute renal failure, uncompensated metabolic acidosis, total bilirubin in excess of 17 and severe coagulopathy.[13] Therefore, timing of OLT in fulminant hepatic failure is best determined by the factors identified by O'Grady: PTT greater than 100 sec, duration of jaundice in excess of 100 days, factor 5 levels less than 30 percent normal.[14] The five-year survival rates are in excess of 75 percent[15,16] even in these desperate circumstances.

With inborn errors of metabolism, transplant should only be considered if the disease state is confined to the liver parenchyma, if the impact of the metabolic error is corrected by normal synthetic function of the transplanted liver, and if the extrahepatic complications of the disease do not contraindicate transplant themselves. Transplantation of the liver in pediatrics is rarely done for malignancy, though may be performed for a nonmetastatic, liver-based tumor, usually hepatoblastoma.

Absolute contraindications to liver transplantation are limited and as follows: seropositivity for human immunodeficiency virus, uncontrollable sepsis of nonhepatic origin, life-threatening disorder of extrahepatic origin, extrahepatic malignancy, irreversible multiorgan system failure, and irreversible significant central nervous system injury.

Preoperative Evaluation

Most centers use a multidisciplinary team approach to evaluate a potential recipient. The medical assessment includes an evaluation of current liver synthetic function, concomitant disease, systemic effects of liver disease, immunization history and nutritional evaluation.

Routine chemistries, infectious disease evaluation (Hepatitis, HIV, CMV, EBV) ABO typing, and liver imaging (Doppler ultrasound, CT and possibly liver biopsy) are all part of the preoperative work up. For patients younger than 17 years of age, UNOS regulations classify patients as status 1 who require ICU management and any hospitalized child with a metabolic disease resulting in increased ammonia or toxic metabolites that cause CNS dysfunction.

Allocation of the liver is based on matching donor and recipient blood groups and body weight. Major HLA histocompatibility matching is not needed as in other organs. An organ is declared unsuitable for transplant when there is a history of major hemodynamic instability, liver ischemia or trauma, systemic infection, diabetes or hypertension in the donor. Positive serologies for HIV, Hepatitis B or C also preclude transplantation. The harvested organ is preserved in University of Wisconsin Solution and can be transplanted upto 24 hours after procurement.

Recipient Hepatectomy

Recipient hepatectomy is the most challenging part of the operative procedure. Portal hypertension with multiple large variceal vessels places the patient at risk for massive hemorrhage. In the pediatric recipient, there is the additional challenge of small vessels for anastamosis. Diaphragmatic attachments of the left lobe are divided followed by the dissection of hilar portal structures. Subsequent exposure of the right lobe follows and the suprahepatic and infrahepatic portions of the inferior vena cava are isolated, clamped and transected. In children caval interruption is tolerated well and seldom is veno-venous bypass necessary. Following resection of the native liver, hemostasis is achieved before implantation of the donor liver.

Implantation of Donor Liver

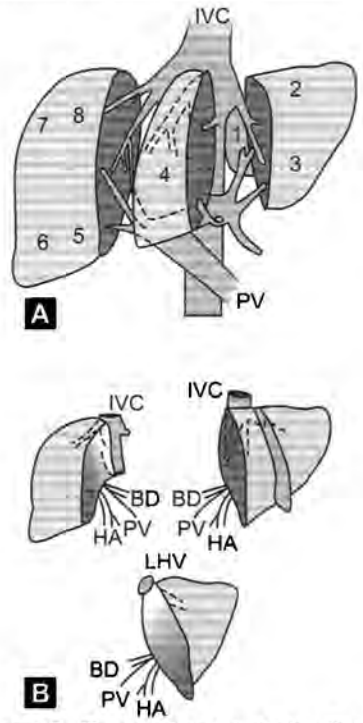
Anastomosis of the vessels is performed in the following order: suprahepatic IVC, infrahepatic IVC, portal vein, hepatic artery, and finally biliary system. Interrupted sutures promote growth of the caval anastamosis. The graft is perfused with portal venous blood while the microsurgical hepatic arterial reconstruction is performed. Microsurgical techniques have been shown superior to grafting with a lower incidence of postoperative thrombosis. Bile duct reconstruction with a Roux-en-Y choledochojejunostomy over an internal stent is performed to an isoperistaltic limb of jejunum.

Prior to re-establishing complete circulation to the newly implanted allografts, hemodynamic and metabolic changes must be anticipated by the anesthetic team. There is a large whole blood volume required upon unclamping to perfuse the transplanted organ and maintain both systemic and splanchnic perfusion. In addition low dose dopamine is frequently initiated. Calcium chloride and bicarbonate are administered to treat the known effect of metabolic acidosis and hyperkalemia from reperfusion of the preserved organ and leaching out of preservation solution into the circulation.

Orthotopic liver transplant from cadaveric donors remains the primary source for both pediatric and adult transplantation at this time. There remains the problem however, of an unacceptable wait time and insufficient number of donors to meet the need of those awaiting transplantation. Whole organ transplantation remains the goal, however, in children and young adults where donor and recipient size is concordant. Optimal graft to body weight ratio range from 1.5 to 3 percent of the recipients weight. Limited supply and increased vascular complications in patients less than 10 kilograms, however, have led to development of techniques to utilize portions of a whole liver in transplantation. The successful transplantation of sections of a whole liver follows from the principle that a component of the liver with vascular and biliary pedicle of sufficient mass can function and sustain life in the same manner as a whole organ.

With reduced-size liver transplantation (RSLT) a potential liver graft is divided into functioning lobes (Fig. 71.1). In pediatric recipients most commonly the left lateral segment or entire left lobe are utilized. Extended right lobe or simple right lobe grafts are frequently too large for smaller children. The heterotopic RSLT was first performed by Fortner and then in an orthotopic fashion by Bismuth.[17,18] Reports of case series followed as the procedure was performed more frequently with survival similar to that of full sized grafts.[19] Of note, however, incidence of surgical complications (biliary leak and bowel perforation) was higher. In 1992, Langas reported no significant difference in survival when comparing RSLT with OLT in pediatric patients operated in an emergent fashion.[20] It would appear then that RSLT then can be performed for young children in a safe manner with no increase in mortality. If the remaining portion of the cadaveric liver is not utilized in another patient, however, the procedure is wasteful of a scare resource and does not increase donor pool allocation. In Europe, where waiting lists for both children and adults are longer than in the United States, *split liver transplantation (SLT)* (Fig. 71.2) procedures are increasingly utilized to improve utilization of adult cadaveric donors. Review of the European Split Liver Registry reveals that 6 month survival rates for elective transplantation in adults was 80 percent and 88 percent for children. When the SLT technique was performed under emergent circumstances, however, both graft and patient survival rates fell (60 and 67% respectively) usually related to complications of the graft (arterial thrombosis, portal venous thrombosis and biliary complications).[21]

Living related liver transplantation (LRLT) is an extension of RSLT in which case the donor is usually a first degree relative of the recipient, most commonly a parent. The first attempt at LRLT was performed by Raia in 1988, and first successfully



Figs 71.1A and B: Types of reduced size liver grafts. IVC—Inferior vena cava; PV—portal vein; BD—bile duct; HA—hepatic artery. Segments are discussed in the text

(Redrawn from Emond JC, Whitington PF, Thislethwaite JR, et al. Hepatoloty 10:867,1989)

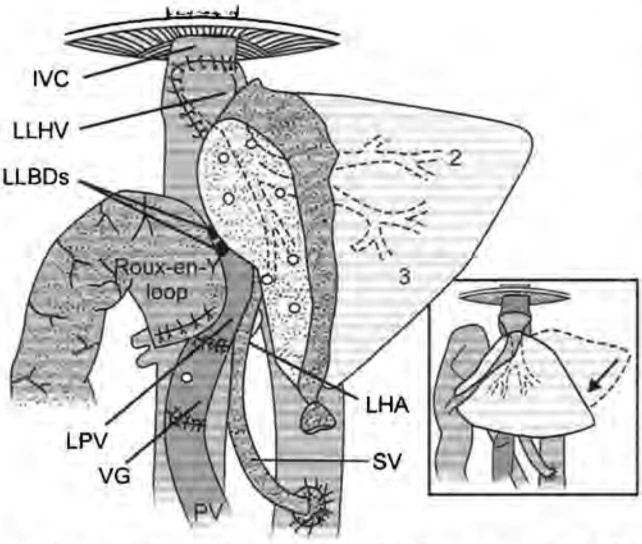


Fig. 71.2: Living related donor left lateral segment after implantation. IVC—Inferior vena cava; LLHV—left lateral hepatic vein; LLBOs—segment 2 and 3 bile ducts; LPV—left portal vein; VG—vein graft; LHA—left hepatic artery: SV—saphenous vein; PV—portal vein; Ao—aorta (inset) Final position of graft after abdominal closure

(Redrawn from Broelsch CE: Whitington PF, Emond JC, et al. Ann Surg 214:428,1991)

completed by Strong one year later.[22,23] Over the last two decades improvement in surgical techniques and increased experience has achieved outcomes equal to those of whole organ or RSLT techniques worldwide.[24-26] Organ procurement in LRLT assumes good donor health and furthermore that donor safety is assured in the operative and postoperative periods. Preoperative screening, both medical and psychia-tric, is performed objectively by a multi-disciplinary team not performing the transplant. Following evaluation, the donor liver anatomy is characterized using CT or MRI and angiography to define both organ volume and vascular supply. Review of data reveals that over 90 percent of potential donors are excluded on the basis of history, physical exam, blood typing or laboratory screening. Only a minority are rejected following an angiography.[27,28] Advantages of LRLT include the selection of an ideal donor in good health, immediate graft implantation and function following procurement, elective surgical intervention, and improved matching of histocompatability loci in donor-recipient pairs with a lower incidence of rejection over time. Since, most donors are parents, however, appropriate weight must be given to the risks inherent to the surgical procedure and potential post-operative complications following donation. To date there has been one donor death following LRLT.[29]

Immunosuppressive Therapy

Immunosuppressive therapy is achieved in a triphasic approach: induction, maintenance, and the treatment of acute or chronic rejection (if necessary). Induction therapy begins in the operating room with implantation and reperfusion and is directed toward achieving a state of profound cell-mediated nonresponsiveness. Immunosuppression is typically achieved with a combination of steroids and calcineurin inhibitors thereby effecting therapeutic state of immunosuppression with fewer side effects than single therapy with either agent could achieve alone. Transition from induction to maintenance is gradual, and adjusted based on the graft function and evidence of rejection.

Calcineurin Inhibitors (Cyclosporine and Tacrolimus) are early cell cycle inhibitors which effect immunosuppression via inhibition of cytokine gene transcription (primarily IL-2) in lymphocytes. Binding of calcineurin inhibitors to FK binding protein interferes with translocation of the nuclear factor from activated T cells required for IL-2 transcription. *In vitro* data suggest that Tacrolimus is 10-100 times more potent than cyclosporine and also interferes with a variety of other cytokines including interferon, TNF, and GM-CSF. Furthermore, it appears to be hepatotrophic which may be beneficial in liver transplants. Oral bioavailability ranges from 5-67 percent with marked variability, and is reduced by food. Tacrolimus undergoes extensive metabolism by mixed function oxidases in the cytochrome P450 group. Most is excreted conjugated in the bile. Measurement of trough levels is helpful for dose adjustment. Cyclosporine (CSA) undergoes extensive hepatic metabolism by cytochrome P450. Pediatric patients have a higher rate of drug clearance than adults. Microemulsion and nonemulsion formulations demonstrate both inter- and intra- patient variability in pharmakokinetics. CSA demonstrates a large volume of distribution and a wide range of trough leves for static dosing regimens. Trough levels are 4l ess predictive of both toxicity and the efficacy of immunosuppression than with tacrolimus.

Of the two oral preparations, the micoremulsion formulation (Neoral) is less affected by bile flow and achieves better absorption.

Although pharmacokinetics and pharmacodynamics differ, toxicity patterns of the calcineurin inhibitors are similar. Hypertension is common, and is mediated through vasoconstriction of the afferent arterioles in the glomeruli with resultant decreases in renal function. The effect is both dose related and reversible (with cessation of the drug or decreases in dosage). Neurotoxicity is common, with upto 50 percent of patients demonstrating headache or tremor. Symptoms occur most commonly during induction and with high trough levels. More serious side effects such as seizures, coma, myopathy, and gray-white matter changes in the cortex also occur though less commonly. Gastrointestinal complaints such as diarrhea, discomfort, bloating, and dyspepsia are frequent. Gingival hyperplasia and hypertrichosis are more common with CSA than tacrolimus. However, tacrolimus has been associated with a higher rate of post-transplant lymphoproliferative disease (PTLD).

Studies comparing efficacy of the two agents have found that patients treated with tacrolimus have fewer episodes of both acute cellular rejection, fewer episodes of steroid-resistant rejection, and a lower cumulative steroid exposure. During induction therapy, trough levels of tacrolimus are maintained at 15-20 ng/ml and 8-10 ng/ml during maintenance immunosuppression. Many centers, however, begin pediatric patients on CSA given their potential increased risk for PTLD with tacrolimus.

Sirulimus is a macrolide antibiotic structurally similar to tacrolimus. Sirulimus binds to FK binding protein as well, however, both T and B cell inactivation follow, resulting in the inhibition of lymphocyte responsiveness and lack of antibody production. Sirolimus inhibits IL-2 production and other cell cycle kinases in the late G1 phase of the cell replication. Following oral administration, absorption is highly variable. Most of the drug is sequestered within the red cells and metabolized at the cytochrome P450 system . The most common side effects reported are thrombocytopenia, leukopenia, and hyper-lipidemia. Most experience with sirolimus is in renal transplant patients where combination with CSA and steroids results in a lower incidence of acute cellular rejection. Early data may suggest that a combination therapy of sirulimus and tacrolimus is effective and allows a steroid sparing effect without overlap of toxicity.

Antilymphocyte antibodies may be either monoclonal or polyclonal preparations which achieve a potent immunosuppressive agent in allograft recipients. Antibodies bind to proteins expressed on T or B lymphocytes. Bound cells are removed from the circulation and down regulation of cell mediated signaling follows. Binding and destruction of the lymphocytes, however, results in the release of a large number of cytokines which typically produce fever, rigors, chills, malaise, and can produce capillary leak, pulmonary edema, hypotension, seizures, and renal failure. Polyclonal antibodies are used primarily in renal transplant patients and bind not only to both T and B lymphocytes, but also to other cellular antigens on RBCs, WBCs, and platelets. Antilymphocyte antibodies provide potent immunosuppression and are very effective at treating steroid resistant acute cellular rejection, however, they are associated with potentially significant side effects, and significantly increase the risk of viral infection and PTLD.

Two preparations of Anti-IL-2 receptor antibodies are available. Both are IgG monoclonal antibodies directed against the IL-2 receptor on activated T cells. Experience and use to date with either preparation is limited.

Mycophenolate mofetil (MMF) is a relatively new agent with antimetabolite properties specific for both T and B cells. The mechanism of action is a reversible noncompetitive inhibition of new purine synthesis. Lymphocytes lack the salvage pathway for purine synthesis and therefore, must synthesize *de novo* purines for cell replication to occur. MMF is administered as a prodrug which must be activated in the liver. Metabolism occurs within the liver as well via conjugation and is excreted in the bile, where it may undergo enterohepatic recirculation. MMF is highly protein bound. Toxicity is largely gastro-intestinal (diarrhea, nausea, and abdominal pain) leukopenia has also been reported.

Steroids have been the mainstay of most immunosuppressive regimens for many years. Side effects of high dose therapy and long-term usage have been decreased when steroids have been used in conjuction with other agents. Steroids act primarily on T-cells activation to inhibit production of T-cell cytokines (IL-1, IL-2, and interferon). It is these cytokines which are necessary to stimulate both macrophage and lymphocyte responsiveness. Following down regulation of effector cells, delayed hypersensitivity is depressed and antibody-dependent cytotoxicity is blocked. Through the general anti-inflammatory actions of steroids, neutrophil migration and activation is decreased and T-cell sequestration in lymphocyte tissue is stimulated.

Postoperative Complications

Primary Nonfunction (PNF)

PNF implies the absence of metabolic and synthetic function immediately following transplant. The reported incidence of PNF varies from 5-10 percent and patients typically present with coma, acidosis, massive coagulopathy, acute renal failure, hypoglycemia and shock. Survival depends upon immediate retransplant and intervening intensive care including plasmpheresis. Immediate post-transplant immunologic events such as antibody mediated hyperacute rejection have been associated with PNF.[30,31] Other donor, recipient, and transplant factors have also been shown to increase the risk (Table 71.2).[32]

Rejection can be acute or chronic:

Acute cellular rejection occurs in 50-65 percent of patients following OLT. Patients may present with fever, abdominal pain, decreased bile synthesis, increased transaminases and decreased synthetic function. Left untreated acute rejection progresses to fulminant hepatic failure. The administration of FK506 is associated with a lower rate of acute rejection than is cyclosporine in children.[33] Biopsy is necessary to confirm the diagnosis. Histopathology reveals endothelitis, portal triad lymphocytic infiltration with bile duct injury and parenchymal cell damage.[34] Acute rejection is usually successfully treated with a cycle of high dose steroids. For resistant rejection, FK506, or alternatively OKT3 can effect a cure in upto 90 percent of cases (Table 71.3). *Chronic rejection* occurs in about 5-10 percent of pediatric patients following transplant. Cases are

Table 71.2: Factors increasing the risk of primary nonfunction

Donor factors
- Injury to donor organ prior to harvest
- Anemia, hypoxia, hypotension
- Severe biochemical abnormality in the donor
- Prolonged cardiovascular compromise prior to donor declaration
- Donor organ steatosis greater than 60 percent macrovasicular fat

Transplant factors
- Prolonged cold ischemic storage (greater than 12-18 hours)
- Prolonged warm ischemic time at implantation (greater than 60 min)
- Complex vascular anastomosis requiring surgical revision
- Significant size discrepancy.

Recipient factors
- Postreperfusion hypotension
- Vascular thrombosis
- Immunologic factors
- ABO incompatible

Table 71.3: Acute cellular rejection

Clinical Symptoms
- Spiking fever
- Lethargy
- Jaundice
- Dark urine and light stools
- Pruritis
- Ascites
- Anorexia

Biochemical Factors
- Increased bilirubin
- Increased transaminases
- Increased alkaline phosphatase
- Coagulopathy
- Decreased albumin

Histopathologic Features
- Mixed portal inflammatory infiltrate, predominantly mononuclear
- Portal and central vein endothelitis
- Bile duct damage

Table 71.4: Chronic rejection

Clinical Symptoms
- Unresolved acute rejection
- Progressive jaundice
- Pruritis

Biochemical Features
- Cholestasis
- Cholangitis
- Variable synthetic function

Histopathologic Features
- Interlobular bile duct injury out of proportion to cellular infiltrate
- Ductopenia
- Subintimal foam cell arteriopathy
- Fibrointimal hyperplasia
- Centrolobular necrosis and fibrosis

typically characterized by progressive cholestasis and elevated transaminases. Chronic rejection may also present after unsuccessful treatment for acute rejection. Both in clinical course and by histopathology, chronic rejection may take on one of two forms. The first is usually seen early post-transplant. Biopsies reveal rejection cholangitis. Response to therapy is poor and patients develop progressive ischemic injury to both bile ducts and hepatocytes with resultant ductopenia and ischemic necrosis. Definitive treatment requires retransplantation. Delayed chronic rejection presents with injury to the biliary epithelium resulting in biopsies wit ductopenia but no ischemic changes.[35] Rescu therapy with FK506 is effective in up to 80 percer of cases[36] (Table 71.4).

Hepatic Complications

Hepatic Artery Thrombosis

Hepatic Artery Thrombosis (HAT) is reported upto 30 percent of pediatric liver transplants.[37] Incidence far exceeds that of adult transplant grou (three to four times as common) and is related vessel diameter and split liver techniques. Patier usually present with fulminant graft failure, seps and biliary leak within the first month followi transplant.[40] Doppler studies are usually diagnos but occasionally angiography is necessary to confi the diagnosis.[41] Thrombectomy with vascu reconstuction if performed early is usually curati Small patients and those requiring complex arter reconstructions are at increased risk. Mazaferr evaluation of a series of 66 pediatric patie identified 5 factors associated with an increased r of HAT: the number of times anastamoses w revised, use of iliac or aortic conduits, intraoperat transfusion of fresh frozen plasma, postoperat anticoagulation, and an arterial diameter less tha mm[42] (Table 71.5).

Portal Vein Thrombosis

Portal vein thrombosis occurs much less comm than HAT, in general, in less than 10% of cases. Tl are usually related to anatomic considerations (suture line too tight, kinked anastamosis), or existing abnormalities of the portal venous bed Patients usually present with graft dysfunt ascites, and upper gastrointestinal bleeding. D nosis is confirmed by ultrasounds and throm tomy is required.

Table 71.5: Factors associated with an increased of hepatic arterial thrombosis

- Donor or recipient size less than 10 kilograms
- Allograft type (LRLT > RSLT > OLT)
- Repeated surgical attempts at anastomosis
- Allograft injury (ischemia, rejection, increased vas resistance)
- Recipient hypotension
- Hypercoagulability

Biliary Tract

Probably the most common and heterogeneous group of complications occur in the biliary system and include leaks, strictures and obstruction. Incidence depends on the size of the patient and the type of graft surgery from 7-20 percent.[47,48] Most patients present with cholangitis. Diagnosis should prompt evaluation of hepatic arterial patency since, the biliary system depends entirely upon blood flow from the hepatic arterial system. Technical errors and graft ischemia account for the majority of early biliary leaks. Strictures represent the other major post-operative complication. Treatment may be either with balloon repair or surgical revision.

EXTRAHEPATIC COMPLICATIONS

Postoperative renal complications are common. Acute renal insufficiency may be a result of preoperative hepatorenal syndrome, ATN, hypovolemia, or secondary to immunosuppressive or nephrotoxic medications. Most patients on cyclosporine or FK 506 in fact have an impaired GFR. Calcineurin toxicity is largely manifest with hypertension secondary to afferent arteriolar vasoconstriction which results in a decreased GFR and an increase in BUN and creatinine. This is dose dependent and usually reversible with dose adjustments. Life-threatening gastrointestinal complications from an upper or lower GI bleed may occur in the transplant patient either from coagulopathy, bleeding from vascular anastamosis or surgical site, gastritis, peptic ulcer disease (stress ulcers), or variceal bleeding. Bleeding varices in a patient following OLT should initiate a work up to rule out a portal venous thrombus. Bowel perforation or obstruction may also occur as with any major abdominal surgery. Atelectesis, pleural effusion, and pneumonia in the postoperative transplant patient are common. Elevation of the right hemidiaphragm may represent injury to the phrenic nerve from compression during traction to expose the hepatic capsule. Finally, seizures are common and usually related to calcineurin toxicity. Toxicity may be related to high-levels from decreased elimination or alternatively, it has been described that calcineurin inhibitors especially FK506 may cause damage to the brain parenchyma with destruction of both gray and white matter and loss of normal gray-white differentiation. Seizure threshold is also potentiated by hypomagnesemia.

The postoperative PICU patient is always at increased risk for infection, and commonly with multidrug resistant organisms or unusual pathogens and the transplant patient is at increased risk. Wound site infections are more common in transplant patients and the risk for infection persists outside the immediate postoperative period secondary to profound immunosuppression following OLT. Bacterial infections immediately following surgery are usually caused by Gram-negative rods. Fungal (*Candida*) and viral (CMV, EBV, HSV) infections present serious risks in these immunocompromised hosts. The major risk factor for active CMV disease is seronegativity at the time of transplant, that is the seronegative patient who receives a CMV positive graft. Reactivation of dormant virus, however, may also occur in the seropositive patient. Pediatric patients are therefore, prophylaxed with gancyclovir during induction immunosuppression to decrease the risk for active CMV disease.[49]

Post-transplant Lymphoproliferative Disease (PTLD)

With profound immunosuppression, the use of tacrolimus, and the receptor specific antibodies, there has been an increase in the incidence of EBV associated post-transplant lymphoproliferative disease (PTLD). Cases vary with both the type and degree of immunosuppression from 3-4 percent with CSA to 14-27 percent following treatment with OKT3 (3-154). Through suppression of cytotoxic T cell activity, a host may become infected with EBV or reactivate dormant virus. PTLD may present as FUO, lymphadenopathy, hepatosplenomegaly, GI bleeding, or upper airway obstruction with graft dysfunction. Histology of involved tissue (lymph nodes, GI tract, or liver) ranges from localized polyclonal lymphocyte proliferation to monoclonal malignant lymphoma. Treatment involves decreasing immunosuppression and gancyclovir. Occasionally chemotherapy may be necessary in cases of frank malignancy. Despite therapy, mortality may achieve 60 percent in cases of monoclonal proliferation.[50]

OUTCOME OF LIVER TRANSPLANTATION

Over the last decade improvements in split liver and vascular techniques, and immunosuppression have decreased waiting time, increased survival and improved allocation in liver transplantation. Overall pediatric survival is presently 88 percent.[51] The greatest improvement in outcome is in infants and patients less than 10 kg in which survival has increased from 50 to 90 percent. Improved survival has been associated with lower infectious, surgical and rejection complications and overall improved quality of life. There remains, however, a shortage of available grafts for transplant. Ongoing research with alternative therapies such as xenogeneic transplantation, transplantation of hepatocytes rather than solid organ, and immunosuppression should continue to improve outcome and decrease morbidity and mortality.

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CHAPTER

72

Liver Transplantation in Children: Indian Scenario

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Liver transplantation (LT) is now the therapy of choice for end stage liver failure, and survival has improved significantly over the last decade with pediatric recipients faring better than adults.[1] This can be attributed to improvement in surgical techniques, better postoperative care and newer immunosuppressive drugs.[2] Over the years, there has been a phenomenal growth in this field in the developed countries and 1 and 5 years survival rates have now increased to 90 and 80 percent, respectively.[3,4] This success of LT has increased the awareness of this treatment modality in the developing world.[5] Successful LT in both children and adults have now been reported from India.[6,7]

The Need

Every year, approximately 2-3 pediatric liver transplants are performed per million population in the West. At this rate, around two to three thousand children would need liver transplantation in India annually. As in the West, extrahepatic biliary atresia (EHBA) is the commonest indication. Nearly 60 percent of children requiring LT at our center had EHBA (Table 72.1). In the Indian scenario, however, most children with EHBA are either diagnosed late or have not undergone the Kasai procedure at all. At another tertiary level center, nearly 70 percent babies with EHBA required LT based on internationally accepted criteria.[8]

INDICATIONS

End Stage Liver Disease

Among those with EHBA, all children with failed Kasai's procedure warrant transplant as also those not operated due to late referral. In other conditions leading to chronic liver failure including biliary cirrhosis, alpha-1-antitrypsin deficiency, chronic active hepatitis and Wilson's disease, the precise prediction of need for LT is difficult. Accepted criteria include evidence of decompensation (fall in albumin, prolongation of prothrombin time), persistent rise in bilirubin, refractory ascites, repeated variceal bleeding, encephalopathy and growth failure in children (Table 72.2).[9] With improved results, transplantation is also now performed for some children to improve quality of life such as profound lethargy and intractable pruritis. Children should ideally be referred to the transplant center before significant hepatic complications (such as variceal bleeding and encephalopathy) and impairment of growth and development set in.

Fulminant Hepatic Failure

Prior to considering LT in FHF, it should be assessed whether spontaneous recovery is possible and if not, is a transplant feasible. Further, irretrievable

Table 72.1: Liver transplantations (1/10/97 to 31/12/07)

Satisfying criteria	234
Neonatal cholestasis syndrome	147
Fulminant hepatic failure	39
Cryptogenic	24
Wilson's disease	06
Hepatoblastoma	05
PFIC	05
Tyrosinemia	04
Hepatocellular carcinoma	02
Budd Chiari syndrome	02

Table 72.2: Indications for LT in end stage chronic liver failure

Clinical parameters	
Recurrent variceal bleeding	Refractory ascites
	Intractable pruritus
	Growth retardation
	Unacceptable quality of life
Laboratory parameters	Prothrombin ratio (INR) >1.4
	Indirect bilirubin > 6 mg/dl
	Albumin < 3.5 mg/dl
	Cholesterol < 100 mg/dl

Table 72.3: Criteria for liver transplantation in fulminant hepatic failure

For paracetamol poisoning
Arterial pH < 7.3 or the following three factors:
Prothrombin time > 100 sec
Creatinine > 3.5 mg/dL
Grade III or IV encephalopathy

For other causes
Prothrombin time > 100 sec or any three of the following:
- Prothrombin time > 50 sec
- Bilirubin > 17.5 mg/dL
- Age < 10 years
- Cryptogenic or drug induced
- Jaundice for more than 7 days before onset of encephalopathy

complications, which preclude a transplant, should be ruled out (Table 72.3).[10] Static variables like age (better prognosis in those between 10 and 40 years of age) and etiology (better prognosis in those with hepatitis A and acetaminophen toxicity) affect the outcome of FHF in addition to certain dynamic variables.[12] The degree of encephalopathy is closely related to the possibility of recovery, 40-50 percent in grade III and 20 percent or lower in grade IV. Fulminant hepatic failure is a rare condition in children, although it is associated with a significant mortality without transplantation, hepatitis A is the commonest cause of FHF in children.[11]

Metabolic Disorders

The indications for LT in these diseases are:
- Acute or chronic liver failure
- Hepatic malignancy
- Extrahepatic effects of disorders, which are reversible completely or partially by transplantation
- Criggler-Najjar syndrome type I, primary oxalosis, urea cycle defects and propionic acidemia.

Assessment

Selection of patient, preparation and proper timing of transplantation are as important as the surgery. LT should be considered for any child with end stage liver disease with a predicted survival of less than one year.

The aims for assessment for LT are:
- To confirm the diagnosis and severity of disease
- To define the patient's general medical status
- To determine eligibility and priority for transplant
- To arrange interim supportive care
- To assess socioeconomic and educational status of the family.

Hepatic function is assessed by measurement of albumin and prothrombin time (synthetic function) and bilirubin, transaminases, alkaline phosphatase and gamma glutamyl transpeptidase. The vascular anatomy is delineated by Doppler ultrasonography and/or MR or conventional angiography. A nutritional, developmental, cardiac and dental assessment is performed in all children. Serological examination is performed to document immunity to viral pathogens.

Preparation for LT

The important aspects of the preparation are:

Nutritional rehabilitation: Recent data suggests that preoperative nutritional status is an important factor affecting outcome following LT. Modular feeds allowing protein, carbohydrate and fat content to be individually prescribed for each child are recommended.

Immunization: It is essential to make sure that routine immunizations are complete. If necessary, immunization for MMR and varicella should be brought forward. However, in children undergoing emergency liver transplants, completing the immunization with live vaccines is not possible.

Treatment of hepatic complications: Ascites and fluid retention is managed by restricted sodium and fluid intake and the use of diuretic therapy. Bleeding varices are treated with intravenous somatostatin or octreotide, endoscopic band ligation or transjugular intrahepatic portal shunts. It is preferable to employ band ligation instead of sclerotherapy because of the potential risk of portal vein thrombosis and ulceration. Hepatic encephalopathy is treated by low-protein diet and oral lactulose. The role of branched chain amino acids remains controversial and use of extracorporeal liver assist devices as a bridge to transplantation is not yet fully established.

Counseling: Education and counseling of the family and the child is of paramount importance to sustain them through the stressful procedure, the prolonged postoperative period and the life-long immunosuppressive therapy with its attendant risks and side effects.

Critical Care Issues in Management

Care of a child after liver transplantation involves a dedicated transplant team. Main issues revolve around graft function in the postoperative period (PT (INR), PTT and other liver function tests) in addition to maintenance of hemodynamic parameters, intake output, abdominal drain output, biliary output and oxygenation to ensure adequate blood flow to liver graft. Strict aseptic precautions must be followed in caring for transplant patients. Primary nonfunction must be closely monitored for in the first 24 hours (rising transaminases, profound hypoglycemia and acidosis, coagulopathy, oliguria) requiring emergency retransplantation. Hyperacute rejection is rare but can occur (humoral rejection). Five to twenty percent patients will have vascular occlusion with accompaying graft loss.Vena cava, portal vein and more commonly hepatic artery may get occluded by intramural thrombus, or less commonly by extrinsic compression or vessel kinking. Vessels smaller than 3 mm diameter tend to have higher incidense of arterial thrombosis. Signs and symptoms consist of FHF, increased transaminase and bilirubin levels with worsening coagulopathy. Portal thrombosis presents with fulminant necrosis, intestinal edema with ascitis. Doppler ultrsonography and angiography are useful tools. Bile leak and postoperative bleeding must be closely monitored. Early nutrition is important. Acute rejection occurs in first few weeks after transplantation (average 23 days after transplant in children) characterized by fever, increased bilirubin and liver enzyme levels and encephalopathy.

The usual immunosuppressive regimen consists of Calcineurin inhibitors – Cyclosporine or Tacrolimus and prednisolone along with Mycofenolate mofetil (MMF). Tacrolimus based immunosuppression is preferred as it has been associated with less acute rejection and better long-term graft survival rates.

Duration of mechanical ventilation in transplant recipient depends upon age and preoperative condition of the patient. A child with fulminant hepatic failure may require a longer duration of ventilation depending on the neurological state. On the other hand, patients with normal pulmonary function preoperatively may require short term or no ventilation. Infants and small children are more likely to need postoperatve ventilation. Ventilatory management aims at avoiding the respiratory complications of atelectasis, effusions and pneumonia. Some smaller patients may require a higher end expiratory pressure to compensate for a distended abdomen pushing onto the diaphragm. In a single center series the mean time to extubation was 11.1 ± 15 hours and the mean duration of ICU stay was 7.2 ± 5.5 days.[12] Pain control is commonly achieved by opioid infusions titrated to effect. Judicious use of muscle relaxants might be needed. Atracurium (a non-depolarizing muscle relaxant metabolized by non enzymatic hydrolysis (Hoffman elimination) can be safely used. General principles of respiratory care apply in all mechanically ventilated patients (see Chapter on Respiratory Care).

Close monitoring, early detection and treatment of complications remains the key to success in addition to supportive management by the liver transplant team.

Indian Scenario

Till a few years back, in the absence of LT facilities in India, a patient with liver failure had only two options, certain death or travel abroad for a transplant. Receiving a liver transplant in the West was not only a costly exercise but also entailed a long waiting period as being a foreigner, he/she would get a low priority on the cadaver waiting lists which were understandably biased to favor the state health entitled native population. The development of liver transplant program in India led to an overall improvement in level of care in allied specialties (anesthesia, critical care, blood bank, radiology, histopathology) on one hand and on the other helped save precious foreign exchange.[6,7]

Our experience over the last 10 years has shown that it is possible to establish a program but there are certain unique hurdles that need to be overcome.[6,7,13] The social evaluation in our setting is extremely important. Low socioeconomic and educational levels along with an unstructured family and insufficient social assistance have a considerable impact on practicality of a transplant taking place, the follow up and overall outcome of patients undergoing transplantation in India.[8] Most patients are referred late for a transplant, quite often when they are not transplantable (Table 72.4). The sub optimal management of the patients in the pre transplant phase results in a sizeable number being unfit for transplantation.[7,13] Cost is still a formidable problem for most patients and absence of medical insurance and state funding further aggravates the problem. Besides, there is a clear bias against the girl child with most families hesitating to spend on transplantation for a girl (Table 72.5). There is a paucity of reliable cadaver organ supply primarily due to low awareness about organ donation. This has necessitated the development of living related liver transplantation.

Table 72.4: Liver transplantation – Assessment details

n = 234	
Unfit	122
Neonatal cholestasis syndrome	94
Infection	65
Malnutrition	94
FHF	28
Ataxia	01
Sepsis	13
Multi organ failure	14

Table 72.5: Liver transplantations (1/10/97 to 31/12/07)

Fit for transplant	112
Refused (Girls 56, Boys 12)	68
Economic factor	61
Willing	44
Cadaver only	21
LRLT	23
Transplants performed	23*
Cadaver	02
LRLT	21

* One re-transplant

Longest follow up 91/2 year

The present day scenario in India has totally changed with patient survival rates comparable to the best centers in the world.[13,14] Over the last decade, 23 transplants have been performed at our center, with another 36 transplants undertaken in nine other centers across the country. The year 2006 was water shed in terms of the learning curve being rewritten. We have recorded 100 percent survival rates in all eight pediatric liver transplants since then.[14] The surgical expertise gained over the last few years combined with the advancements made and lessons learnt in the medical management have contributed in a big way to this achievement. Despite these success stories, there is still a lack of awareness on existing liver transplant facilities in India even within the medical fraternity.

With an appropriate brain death law already in place, sufficient public and professional education is needed to develop cadaver donation. However, with excellent results of LRLT's, this problem is somewhat offset till the time there is more awareness and acceptability towards organ donation in our country. A pediatric LT at our center costs between 12 to 15 lakhs, which is roughly one-tenth of what it would cost in the West. Despite these huge difference in costs, contributions from philanthropic organizations and medical insurance are required if LT is to become available to the vast majority of patients in India. Finally, it is the faith and support of the medical fraternity and the public at large that can help our endeavors to make LT a practically feasible and economically viable treatment modality in India.

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Section Six

Hematological Issues

CHAPTER
73

Disseminated Intravascular Coagulation

Rajesh Mehta, Prashant Pruthi

Disseminated intravascular coagulation (DIC) is a complex thrombo-hemorrhagic condition characterized by widespread activation of coagulation, which results in generation of intravascular fibrin and consumption of procoagulants and platelets. Both thrombotic (Procoagulant activation) and bleeding (Fibrinolytic activation and consumption coagulopathy) manifestations are hallmark of this disorder. Intravascular coagulation resulting in this disorder can compromise the blood supply to various organ systems like pulmonary, renal, hepatic and the central nervous system, which in conjunction with hemodynamic and metabolic derangements may contribute to failure of multiple organs. DIC occurs in acute and chronic forms depending on intensity and continuity of activation stimuli though the pathophysiology is same. DIC is not a primary disease, it always occurs secondary to an underlying disorder. As the sequalae of DIC can be devastating, early clinical suspicion and laboratory diagnosis is essential.

Associated Clinical Conditions

DIC is an acquired disorder that occurs in a wide variety of clinical conditions, which are listed in Table 73.1.

Table 73.1: Common clinical conditions associated with DIC in children

1. Infections
   - Bacterial (Both Gram –ve and Gram +ve, and Rickettsia)
   - Viral (e.g., HIV, Cytomegalovirus, Varicella, Hepatitis)
   - Fungal (e.g., Histoplasmosis, Aspergillosis)
   - Parasitic (e.g., Malaria, Kala azar)
2. Malignancies
   - Hematological (e.g., Acute Myelocytic Leukermia)
   - Metastatic
3. Trauma
   - Serious tissue injury
   - Head injury
   - Fat embolism
4. Immunologic disorders
   - Severe allergic reactions
   - Hemolytic transfusion reaction
   - Transplant rejection
5. Reaction to toxins (e.g., snake venom, drugs)
6. Burns
7. Vascular disorders
   - Giant hemangioma (Kassabach-Merritt syndrome)
   - Aortic aneurysm
   - Collagen vascular disorders
   - Hypoxia and hypoperfusion
8. Neonatal causes
   - Asphyxia
   - Hypothermia
   - RDS
   - NEC
   - Abruptio placentae

Infectious Causes

Infectious disease, particularly septicemia, is the most common underlying disorder leading to DIC. Although any microorganism can cause disseminated intravascular coagulation, bacterial infections account for most of reported cases. Clinically overt disseminated intravascular coagulation may occur in 30-50 percent of patients with gram negative sepsis.[1-3] In an Indian study in pediatric patients, 60 percent cases of DIC were attributed to septicemia.[4] Triggers for the activation of diffuse coagulation in patients with infection are cell specific membrane components like lipopolysaccharides, endotoxins or exotoxins.

Malignancies

Both hematologic and solid tumors can initiate continuum of events in coagulation pathways leading to DIC. Fifteen percent of patients with acute leukemia and ten to fifteen percent of patients with metastasized tumors have evidence of disseminated intravascular coagulation.[5-6] Acute promyeloytic leukemia is characterized by a severe hyperfibrinolytic state in addition to an activated coagulation system.

Trauma

The incidence of DIC in the patients with severe trauma, who develop systemic inflammatory response syndrome as consequence, is 50-70 percent.[3-7] A combination of mechanisms, including the release of fat and phospholipids from tissues into circulation, hemolysis and endothelial damage may contribute to systemic activation of coagulation in these patients.

Giant Hemangiomas

Giant hemangiomas and large aortic aneurysms may result in local activation of coagulation,[8] which may result in systemic depletion of locally consumed coagulation factors and platelets leading to DIC. The incidence of clinically overt DIC is 25 percent among the patients with giant hemangiomas whereas the incidence is approximately 0.5-1 percent among patients with large aneurysms.[8,9]

Miscellaneous Activating Stimuli

Cytotoxic antigen-antibody reactions play an important role in DIC associated with acute anaphylactic reaction, purpura fulminans and transfusion of incompatible blood. Snake venoms contain enzymes that may trigger coagulation.

Pathophysiology of DIC

Though pathophysiology of DIC is complex, recent studies have largely clarified it. The systemic formation of intravascular thrombin in this disorder, results from increased generation of thrombin, suppression of anti-coagulation mechanisms and delayed removal of fibrin[10] (Fig. 73.1).

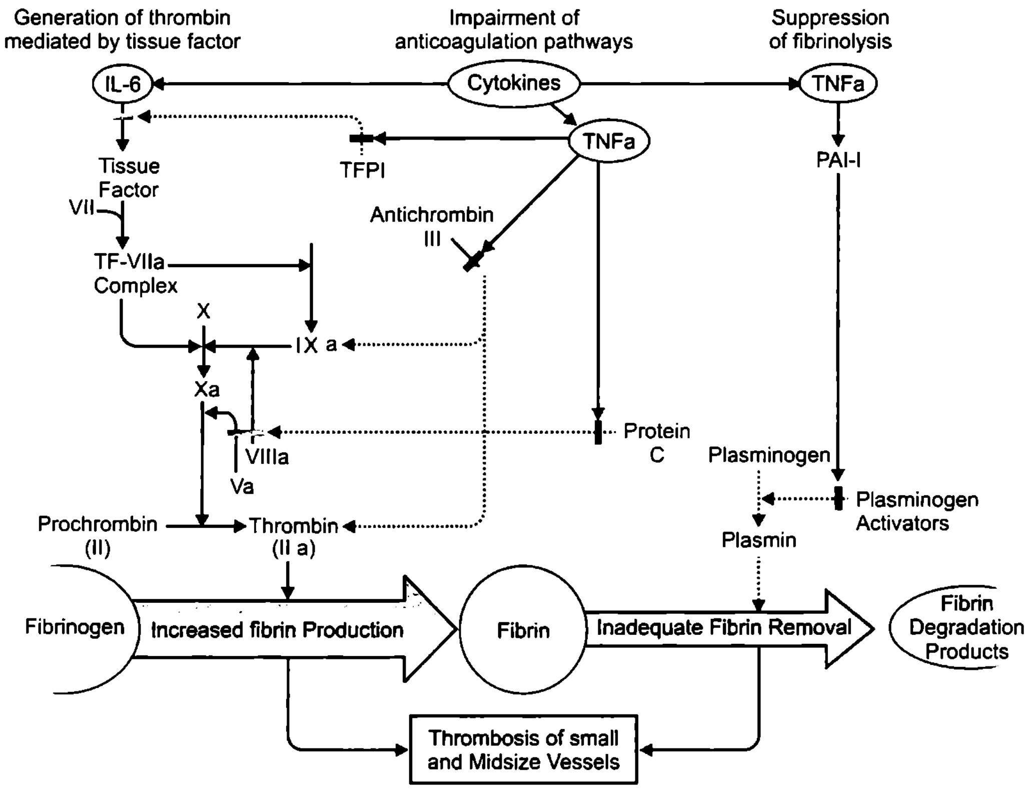

Generation of thrombin mediated by tissue factor
Impairment of anticoagulation pathways
Suppression of fibrinolysis
IL-6
Cytokines
TNFa
TNFa
Tissue Factor
VII
TFPI
PAI-I
Antichrombin III
TF-VIIa Complex
X
IX a
Xa
Protein C
VIIIa
Va
Plasminogen
Plasminogen Activators
Prochrombin (II)
Thrombin (II a)
Plasmin
Fibrinogen
Increased fibrin Production
Fibrin
Inadequate Fibrin Removal
Fibrin Degradation Products
Thrombosis of small and Midsize Vessels

Fig. 73.1: Schematic flow diagram of pathogenesis of DIC (disseminated intravascular coagulation)

As is true for almost all the systemic inflammatory responses, the derangement of coagulation and fibrinolysis in disseminated intravascular coagulation is mediated by pro-inflammatory cytokines.[10,11] These cytokines result in expression of tissue factor on mononuclear cells stimulating extrinsic pathway of coagulation. Interleukin-6 is the primary mediator causing activation of coagulation. Tumor necrosis factor influences the activation of coagulation by its effects on interleukin-6 and plays a very important role in dysregulating physiologic anticoagulation pathways. All major physiologic anticoagulants antithrombin III (important inhibitor of thrombin), protein C (activated protein C proteolyses factor V and VII) and tissue factor pathway inhibitor are decreased or defective in DIC. Fibrinolytic system is also largely suppressed even after activation of coagulation by sustained increase in plasma level of plasminogen activation inhibitor type 1.[12] Thus, a remarkable imbalance between coagulation and fibrinolysis exists, resulting in a net pro-coagulant state. Consumption of coagulation factors and platelets during ongoing coagulation results in increased predisposition for bleeding.

Clinical Features

Other than signs of the underlying disease, approximately 90 percent patients with DIC present with hemorrhagic manifestations. Bleeding of virtually every kind have been described. Commonly, spontaneous bruising or purpura, oozing from venipuncture sites or around catheters and systemic bleeding like gastrointestinal, CNS or pulmonary bleed are seen in most patients. An average patient of DIC bleeds from at least three unrelated sites.[13] Thrombotic manifestations are difficult to recognize clinically and when obvious it commonly involve end organ failure, necrosis of skin and subcutaneous tissue and peripheral symmetric gangrene.

Diagnosis

Both being a bleeding and a thrombotic disorder, DIC can't be established or ruled out by any single test. However, a combination of test results, in a patient with clinical condition known to be associated with DIC can be used to diagnose this disorder with reasonable certainty. It is usually diagnosed when with an underlying disease, initial platelet count is less than 1,00,000 per ml, clotting tests are prolonged and fibrin degradation products are present in the plasma. Tables 73.2 and 73.3 summarize the common clinical and specialized laboratory tests for DIC.

Severe liver disease may have same characteristic abnormalities as DIC. Circumstantial findings like portal hypertension, cirrhosis and lack of worsening of coagulation abnormalities on follow-up indicate liver disease. Blood smear finding of schistocytes and fibrin deposits in vessels on organ biopsies are characteristic findings of DIC.

Treatment

The first essential step and cornerstone of management of DIC, after ensuring initial stabilization

Table 73.2: Common clinical laboratory tests

Prothrombin time:	Tests the extrinsic and common pathways. 50-75 percent patients have prolonged values. Occasionally it may be reduced/normal due to presence of circulating activated coagulation factors.
Activated partial Thromboplastin time:	Test for intrinsic and common pathway. 50-60 per cent patients have prolonged values.
Thrombin time:	Measures conversion of fibrinogen to fibrin. It is usually prolonged.
Fibrin degradation	Levels elevated in 85-100 percent patients. Products: Commonly done by latex agglutination test.
D-dimer assay:	D-dimer is generated by plasmin lysis of cross-linked fibrin clots. Documents the presence of thrombin (cross linking) and plasmin (fibrinolysis). Elisa kits are readily available.
Protamine test:	Paracoagulation test detects fibrin monomers in Plasma. Usually positive in DIC. Also positive in patients with arterial or venous thrombosis.
Platelet count:	Invariably decreased in DIC. Progressive decrease is sensitive for diagnosis but not specific.
Fibrinogen Level:	Usually decreased in DIC. May be increased initially as it is an acute phase reactant.
Blood smear:	Schistocytes seen in 50 percent of patients.

Table 73.3: Specialized laboratory tests (generally neither easily available nor essential)

Anti-thrombin III level:	Usually decreased in DIC. Reliable and useful test for diagnosis, therapeutic monitoring and prognosis
Protein C level:	Usually decreased. More useful for predicting prognosis
Prothrombin fragments F1+2:	Measures generation of thrombin. Assay for detection of prothrombin activity
Thrombin-Antithrombin	Formed when thrombin combines with antithrombin (TAT Complex) during DIC. Better sensitivity and specificity (80-90%)
(TAT) Complex: Fibrinopeptide A	Breakdown product of fibrinogen. Indicative of thrombin activity. Better sensitivity and specificity (80-90%)

(Airway, breathing and circulation), is treatment of underlying disorder. Without this, no treatment would be successful and often after this step no further specific treatment is needed for the coagulopathy. Also there are controversies regarding further steps of treatment, as adequate trials on DIC treatment are scarce because of complexity and unpredictable course of DIC. The clinical picture of simultaneous occurring systematic thrombotic depositions and bleeding make it difficult to decide which therapy to administer.

At present, intervention consists of administration of blood components, anticoagulants or physiological coagulation inhibitors—singly, sequentially or in combination. All these interventions should be done depending on the clinical condition of the patient. Biochemical abnormalities indicated by laboratory tests alone need no further treatment.

Plasma and Platelet Transfusions

In patients with manifest bleeding and those who are at high risk of bleeding, efficacy of treatment with platelet concentrates or fresh frozen plasma has been reported in various studies.[5,14] However, adequate controlled trials are not available. The only randomized controlled trial in neonates with DIC comparing administration of fresh frozen plasma and platelets with whole blood exchange transfusion failed to show any change in outcome of DIC or survival.[15,16] Despite the lack of evidence, most authors recommend treatment with fresh frozen plasma at least when patients are bleeding or are at high risk for bleeding.[16,17] 10-15 ml/kg of FFP will raise clotting factors activity by 10-15 percent and 1 unit/m^2 of platelet concentrate will increase the platelet count by about 20,000/µl. It is generally agreed that it is reasonable to maintain platelet count of more than 50,000/cmm and a fibrinogen level of more than 1 g/l.[18]

Anticoagulants

Heparin has been shown to have a beneficial effect in small, uncontrolled studies of patients with DIC, but not in controlled trials.[19] However, clinical studies have also not shown any significant increase in incidence of bleeding complications with heparin therapy. So routine therapy with heparin is not advised but heparin is probably useful and indicated in DIC patients with clinically overt thrombosis, for example, purpura fulminans, sacral ischemia or thromboembolism. In such cases low dose of heparin 5 to 8 u/kg/hour is advocated, potentially in combination with plasma. Low molecular weight heparin (having higher anti-factor Xa to anti-factor IIa activity ratio, which decreases bleeding risk) is a safer alternative novel therapy and can be given subcutaneously twice a day.

On continuous infusion the PT (Prothrombin time) may be useful for monitoring coagulation function since it is less affected by heparin effects than TT or PTT (Thromboplastin time or Partial thromboplastin time). A normal or nearly normal PT combined with consistent prolongation of PTT or TT within given limits should indicate control of DIC. In heparin responsive DIC anticoagulation should be maintained until plasma factors and platelet count have stabilized at normal levels.[20]

Recombinant hirudin is a potent and specific direct thrombin inhibitor and unlike heparin, it is independent of anti-thrombin III (AT III). It was reported to be effective in one series of 5 patients with hematological malignancy associated DIC.[21] However, to date, no randomized trial is available.

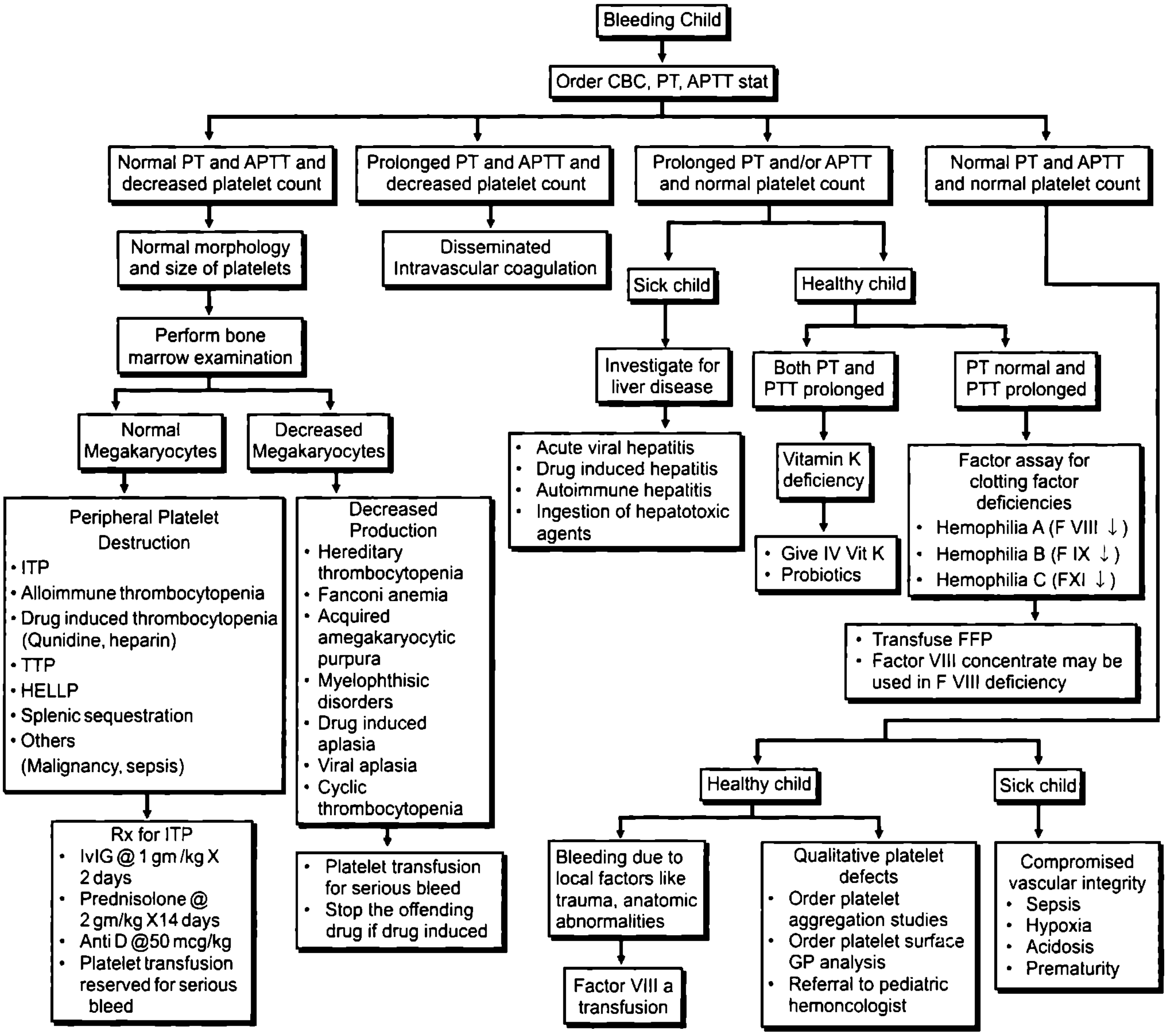
Coagulation Inhibitors

AT III is an important physiological inhibitor of blood coagulation and patients with DIC almost always have an acquired deficiency of anti-thrombin ill. However, till adequate trial are done, this expensive treatment may be considered as a supportive therapeutic option only in patients with severe disseminated intravascular coagulation and where high mortality is expected.[22]

Protein-C concentrate as a treatment modality has been reported to be effective in some case reports recently.[23,24] Thrombomodulin has been shown to be beneficial in animal models of DIC.[25] Clinical trial of inhibitors of tissue factors (TFPI's play a key role in initiation of coagulation) have also recently been initiated but the result are not yet available.

To summarize, the first priority in treatment of DIC, as emphasized above should consist of optimal management of the underlying cause. In case of bleeding or high risk of bleeding, plasma and platelets transfusion is indicated. Clinical and laboratory monitoring should be continued and repeated transfusions can be given depending on level of clotting times.[22] Heparin treatment is reserved only for those patients who present with clinical signs of extensive fibrin deposition like

Flow chart 73.1: Outlines the general approach to any bleeding child in PICU



Bleeding Child
Order CBC, PT, APTT stat
Normal PT and APTT and decreased platelet count
Prolonged PT and APTT and decreased platelet count
Prolonged PT and/or APTT and normal platelet count
Normal PT and APTT and normal platelet count
Normal morphology and size of platelets
Disseminated Intravascular coagulation
Sick child
Healthy child
Perform bone marrow examination
Investigate for liver disease
Both PT and PTT prolonged
PT normal and PTT prolonged
Normal Megakaryocytes
Decreased Megakaryocytes
• Acute viral hepatitis
• Drug induced hepatitis
• Autoimmune hepatitis
• Ingestion of hepatotoxic agents
Vitamin K deficiency
Factor assay for clotting factor deficiencies
• Hemophilia A (F VIII ↓)
• Hemophilia B (F IX ↓)
• Hemophilia C (FXI ↓)
Peripheral Platelet Destruction
• ITP
• Alloimmune thrombocytopenia
• Drug induced thrombocytopenia (Qunidine, heparin)
• TTP
• HELLP
• Splenic sequestration
• Others (Malignancy, sepsis)
Decreased Production
• Hereditary thrombocytopenia
• Fanconi anemia
• Acquired amegakaryocytic purpura
• Myelophthisic disorders
• Drug induced aplasia
• Viral aplasia
• Cyclic thrombocytopenia
• Give IV Vit K
• Probiotics
• Transfuse FFP
• Factor VIII concentrate may be used in F VIII deficiency
Healthy child
Sick child
Rx for ITP
• IvIG @ 1 gm/kg X 2 days
• Prednisolone @ 2 gm/kg X14 days
• Anti D @50 mcg/kg
• Platelet transfusion reserved for serious bleed
• Platelet transfusion for serious bleed
• Stop the offending drug if drug induced
Bleeding due to local factors like trauma, anatomic abnormalities
Factor VIII a transfusion
Qualitative platelet defects
• Order platelet aggregation studies
• Order platelet surface GP analysis
• Referral to pediatric hemoncologist
Compromised vascular integrity
• Sepsis
• Hypoxia
• Acidosis
• Prematurity

venous thrombosis or purpura fulminans. Finally AT III replacement though expensive and still awaiting large trials, can be considered in patients with severe DIC with low levels of circulating AT III (Flow chart 73.1).

Prognosis

Prognosis of DIC depends on the underlying cause and severity of coagulopathy. Assigning a numerical figure for morality is difficult but prospective clinical trials have shown that development of DIC in patients with sepsis or severe trauma roughly doubles the risk of death.[3,26] Recently factor VIIa tranfusion has been used other wise healthy trauma patients with severe bleeding.[27,28]

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CHAPTER

74

Blood Transfusion in Neonatal and Pediatric Intensive Care

Gurinder Pal Singh, RN Makroo, Praveen Khilnani

INTRODUCTION

Transfusion practices in intensive care have become a debatable issue, with the risks becoming more obvious. The liberal transfusion strategy did not bring any reduction in mortality rates, and in fact as the evidence has shown, it leads to more adverse effects and complications. The restrictive transfusion policy has become the choice of late, with individualization of the transfusion, as per the physiological need for transfusion in a given patient.[1]

Determinants of exactly which patients to transfuse remain poorly defined and have been the subject of considerable debate in recent years.[2] Concerns have been raised regarding the safety of blood transfusions, in part due to fears of transfusion- related transmission of infectious diseases such as human immunodeficiency virus (HIV), and more recently bovine spongiform encephalitis. Also it has been observed that blood transfusions may increase the risk of infections, by complex effects collectively grouped under "transfusion-related immunomodulation", immunosuppression, Transfusion associated Acute Lung Injury (TRALI) and Transfusion Related Circulatory Overload (TACO). As a result of these concerns and several studies suggesting better or similar outcomes with lower transfusion triggers or worse outcomes in transfused patients there has been a general decrease in the transfusion threshold from the 10 g/dL hemoglobin concentration widely used in the past, with many physicians now waiting till the hemoglobin concentration approaches 7 g/dL before transfusing.

Often we as intensivist are rendered in situation where the need to transfuse a child with blood component arises, important during those situations is to justify the need on an individual basis, and the current practice is to use the components required than the whole blood. In addition, manipulation of blood products by filtration and irradiation make the products safer for the subsets of patients who require them. This chapter will discuss the concerns while transfusing a child with a blood product, the risks/ benefits of such an intervention, the guidelines in transfusion medicines of critically sick children, and the need for individualization of the transfusion, of every sick child depending upon the disease state, concern regarding oxygen delivery and consumption, and the actual physiological need for transfusion.

Physiological Principles

Knowledge of several physiological differences between the newborn pediatric and adult are prerequisite for effective transfusion therapy in neonates and children. Full-term infants have a blood volume of approx 80-85 ml/kg, while in premature infant, the average blood volume is 90-95 ml/kg. As infant's bone marrow responds more slowly to anemia than a mature marrow, the new born compensates for hypovolemia less well than adults; it responds to 10 percent volume loss by diminishing stroke volume, with increasing heart rate, increasing peripheral vascular resistance to maintain systolic blood pressure and thus with diminished cardiac output, resulting in poor tissue perfusion, low tissue oxygenation and metabolic acidosis. Neonates suffer exaggerated effects from hypothermia, including increased metabolic rate, hypoglycemia, metabolic acidosis and a tendency to apneic episodes that may lead to hypoxia, hypotension and cardiac arrest.[3]

The average hemoglobin concentration of full-term infant at birth is approximately 17-18 gm/dl which is followed by physiological decrease in hemoglobin during the first three months of life. The average hemoglobin concentration in a healthy child from 3 months to 6 years of age is 11.0-12.0 gm/dl and by 7 to 13 years of age the average hemoglobin concentration is 13 gm/dl.[4]

Blood cells metabolize glucose through the glycolytic and hexose-monophosphate shunt pathways, accordingly, lactate, which is the end-product of these metabolic pathways, progressively accumulates during blood storage. As lactate increases, falling pH inhibits glycolytic enzyme activity so that adenosine triphosphate (ATP) and 2, 3-diphosphoglycerate (2, 3-DPG) levels decrease. As intra erythrocytic ATP concentrations fall, membrane lipid is altered and sodium-potassium ATPase-dependent shunts are inhibited, resulting in rigid spherocytic red cells. Some of these cells spontaneously lyse due to increased osmotic fragility, and others lyse *in vivo*. Intraerythrocyte 2, 3-DPG is an important determinant of oxygen affinity and delivery. The reduced 2, 3-DPG levels cause a leftward shift in the oxygen dissociation curve, which results in increased oxygen affinity of hemoglobin and, in turn, poor oxygen offloading at the tissue level. Because of high percentage of fetal hemoglobin, the tissue oxygenation is poor in newborn as compared to older children and adults. Stored cells have low 2, 3-DPG (enzyme essential for oxygenation) and this may cause problems in neonates, as their capacity to compensate for hypoxia is limited in premature newborn infants who have immature immune system resulting in inadequate antibody response. All these physiological changes are well tolerated by normal infants but pose difficulty in premature newborns, seriously ill infants and children.[5]

ANEMIA IN THE INTENSIVE CARE UNIT

Pathophysiology of Anemia (Flow chart 74.1)

We all known that the major concern in anemia is a reduction of oxygen delivery (DO_2), But what is the lowest hemoglobin level and DO_2 (critical DO_2) under which oxygen consumption will fall below the critical level, the question will always be a puzzle to the intensivist. In healthy adults, the critical DO_2 is less than 10 ml of oxygen per kg per minute, a level reached at a hemoglobin concentration of 5.0 g/dL. The critical hemoglobin concentration may be higher in critically ill children for many reasons.[6,7]

1. The basic metabolic requirement of healthy children is higher than it is in adults.
2. The stress experienced by critically ill patients and their disease frequently increases oxygen consumption (VO_2).
3. The critical threshold is shifted to the right in critically ill patients, which may explain why pathologic oxygen supply dependence is seen in some critically ill patients, such as in cases of severe sepsis and septic shock.

Adaptation to Anemia

The next question which we need to answer is the role of body adapting in response to anemia. By two to four fold is the amount of oxygen delivered to the tissue, in excess of the normal requirement in normal individuals. The adaptive processes initiated by the body in anemia are:[8]

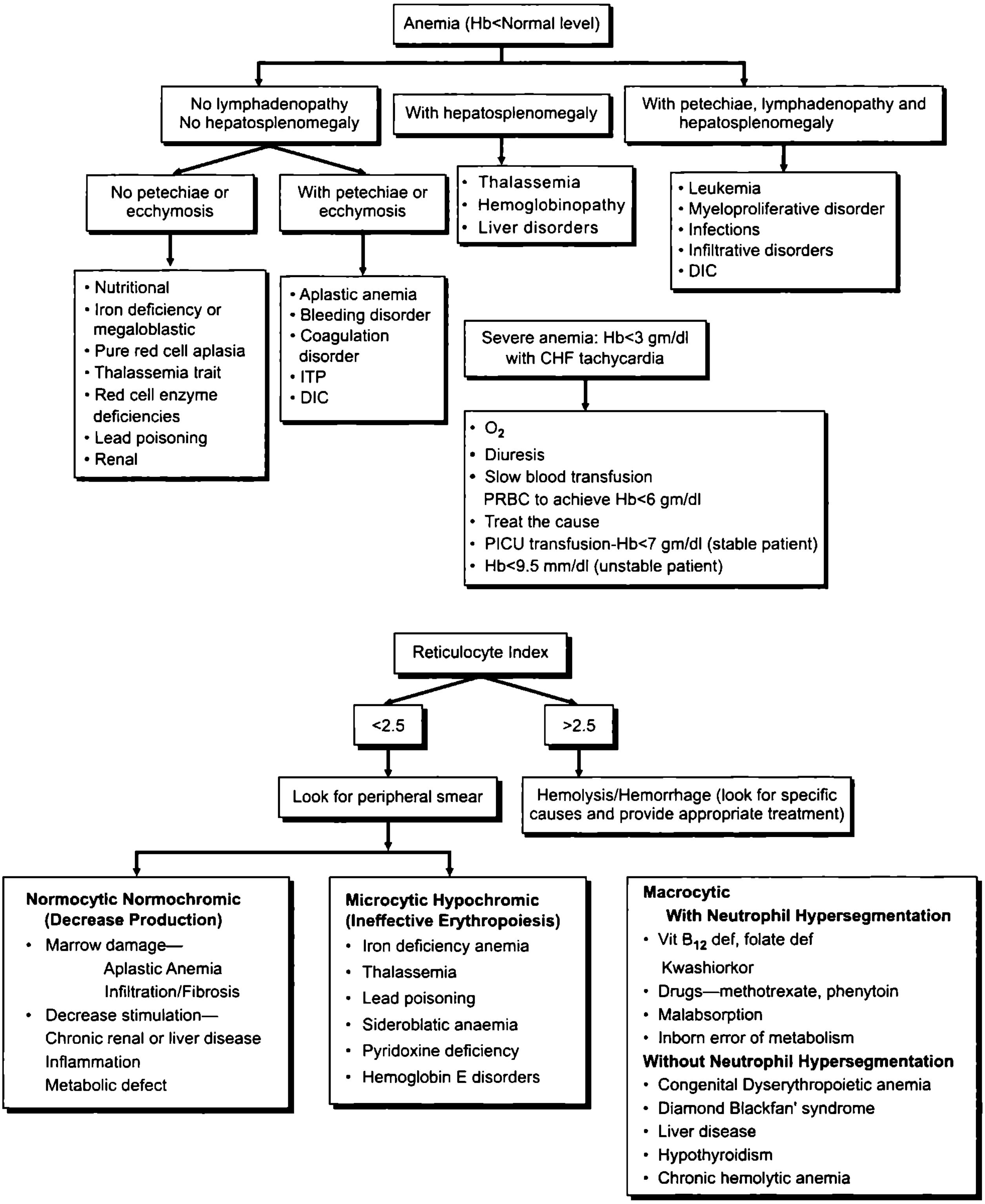
1. increased extraction of available oxygen;
2. increased heart rate, stroke volume, and cardiac output;
3. a redistribution of blood flow from nonvital organs toward the heart and brain, at the expense of the splanchnic vascular bed;
4. a shift to the right in the Oxyhemoglobin-dissociation curve, which means that the oxygen affinity of hemoglobin is decreased:
5. Enhanced erythropoietin production and release to stimulate bone marrow production of RBC's.

Impairment in Adaptive Mechanisms in Newborns and Pediatric Population[9-11]

Because the response to adapting in anemia is different in children than adults, there may be failure of these adaptive mechanisms, the reasons for which are cited below.

Children have lower myocardial compliance, and in addition to that the higher heart rates in children and infants limits the ability to increase cardiac output. Other problems which cause impairment in

Flow chart 74.1: Anemia in PICU


Anemia (Hb<Normal level)
No lymphadenopathy No hepatosplenomegaly
With hepatosplenomegaly
With petechiae, lymphadenopathy and hepatosplenomegaly
No petechiae or ecchymosis
With petechiae or ecchymosis
• Thalassemia
• Hemoglobinopathy
• Liver disorders
• Leukemia
• Myeloproliferative disorder
• Infections
• Infiltrative disorders
• DIC
• Nutritional
• Iron deficiency or megaloblastic
• Pure red cell aplasia
• Thalassemia trait
• Red cell enzyme deficiencies
• Lead poisoning
• Renal
• Aplastic anemia
• Bleeding disorder
• Coagulation disorder
• ITP
• DIC
Severe anemia: Hb<3 gm/dl with CHF tachycardia
• O_2
• Diuresis
• Slow blood transfusion PRBC to achieve Hb<6 gm/dl
• Treat the cause
• PICU transfusion-Hb<7 gm/dl (stable patient)
• Hb<9.5 mm/dl (unstable patient)
Reticulocyte Index
<2.5
>2.5
Look for peripheral smear
Hemolysis/Hemorrhage (look for specific causes and provide appropriate treatment)
Normocytic Normochromic (Decrease Production)
• Marrow damage— Aplastic Anemia Infiltration/Fibrosis
• Decrease stimulation— Chronic renal or liver disease Inflammation Metabolic defect
Microcytic Hypochromic (Ineffective Erythropoiesis)
• Iron deficiency anemia
• Thalassemia
• Lead poisoning
• Sideroblatic anaemia
• Pyridoxine deficiency
• Hemoglobin E disorders
Macrocytic
With Neutrophil Hypersegmentation
• Vit B_{12} def, folate def Kwashiorkor
• Drugs—methotrexate, phenytoin
• Malabsorption
• Inborn error of metabolism
Without Neutrophil Hypersegmentation
• Congenital Dyserythropoietic anemia
• Diamond Blackfan' syndrome
• Liver disease
• Hypothyroidism
• Chronic hemolytic anemia

children include the presence of congenital heart disease, which may limit the ability of myocardium to increase DO_2. Similarly children with cyanotic heart disease may have higher hemoglobin levels which may increase the viscosity of blood higher and thus impeding the microcirculation.

The higher level of fetal hemoglobin in neonates and infants, by shifting the oxygen dissociation curve to the left and by increasing the overall viscosity of the blood may decrease the delivery of oxygen to the peripheral tissues. The erythropoietin which a stimulant for bone marrow to produce RBC's, is secreted in lesser amount from the kidneys of sicker children. The other factor to realize is that children because of their growth issue have more energy needs and thus oxygen demands. Last but not the least, the ability of the children, because of the difference in disease pattern than adults, with children having more fresh systems and less of coronary and other chronic problems, may tolerate lower hemoglobin levels. All these factors should be in the knowledge of the physician or the intensivist, while a decision to transfuse a child is made, so that individualization is made accurately.

Risk vs Benefits[12-14]

Now while discussing about transfusing a child, the most important aspect to be aware of the risks and the benefits of transfusion in that particular sick child. The idea of transfusing a child with anemia is to raise the hemoglobin levels and thus the oxygen delivery. Many studies have reported that stored RBC's have impaired ability to negotiate the microcirculation and thus may cause an actual decrease in oxygen delivery to the tissue at the micro circulation level.

Apart from this the other risks associated may be the transmission of infections, transfusion reactions, leading to activation of the proinflammatory cytokine response, immunosuppression, which may be very important in a patient who is already primed with a systemic inflammatory response syndrome or sepsis.[15]

Other significant complications reported are necrotizing enterocolitis related to the impairment of affection of the microcirculation in the splanchnic bed (Similar events produce gut ischemia in the pediatric and adult patients), and increase propensity to develop retrolenticular fibroblasias in premature babies.

It would always be a difficult option to determine at which level of Hb, the benefit would outweigh the risks, because many of the studies do not support the notion that packed cell transfusion will always improve oxygen delivery, and many outlining that infact this may be decreased also following a transfusion. And all of these issues become much more complicated by the fact that there are limited bedside benchmarks to determine the level of oxygen consumption. The most important question of all at this stage would be, though RBC's transfusion may improve the oxygen consumption of the patient, but what actually has this made change in the mortality and morbidity of that patient and whether the change has been a positive or negative attribute.

The literature in this aspect suggests that if the anemia is severe enough < 5 and if there are associated symptoms like dyspnea and associated features of heart failure, correction of the anemia decreased the mortality[16] (This series is reported from Kenya in 1269 patients of malaria who were hospitalized). In the case of critically sick babies, who were receiving tertiary level care, reported mortality and morbidity was higher in the transfused group than in the non-transfused group, the median hemoglobin at which the transfusion was done was 6.4. The higher morbidity reported was prolonged mechanical ventilation, more days on vasoactive agents, and increased length of stay in the PICU and in the hospital.

Similarly the randomized clinical trial conducted by the Canadian group[17] showed that patients who were transfused only when their Hb fell below 7.0 gm (Restrictive), had lower mortality that patients who were transfused when their Hb fell below 10.0 (Liberal group). Morbidity in the form of multiorgan failure and Nosocomial infections were higher in the liberally transfused than in the restrictive group though not statistically significant. The RBC's used in these trials were not Leukodepleted, which could have led to the activation of the proinflammatory cytokines and the adverse outcomes reported.

The SOAP[18] study where Leukodepleted RBC's were used did not show any statistically difference in the mortality and morbidity of the transfused patients. The TRIPICU has shown that the outcome of stable patients in the PICUs who received more or less red cells was similar. All transfusions were done with leukoreduced RBC's and two threshold were compared (7.0 and 9.5 gm). To summarize, the decision to transfuse a child should be on an individual basis weighing the benefits against the risks and depending upon the kind of disease and its severity and most importantly physiological status of the critically ill child.[19]

Guidelines for Blood Transfusion

Following a review of the available pediatric literature,[20-22] one cannot conclude the actual threshold at which a critically sick child should be transfused, thus the need for individualization the need for that particular child, which would include documenting determinants of transfusions, physician based and institutional practices and the appropriateness of these practices. For example, children with cyanotic cardiac myopathy may need transfusion at even higher Hb level (10-11gm). For the pediatric critical care practitioners, the threshold for transfusing a child varies tremendously, ranging from less than 7.0 gm and above this level to as levels as high as 13.0 gm. Ideal Hb for critically ill child with heart disease is unknown.

The Surviving Sepsis Campaign[23] guidelines for the management of severe sepsis and septic shock are evidenced based guidelines from the adult literature which were published in 2004. Recommendation regarding blood production administration in the septic patient state that following resolution of tissue perfusion and in the absence of significant coronary disease or acute hemorrhage, the critically sick patient should be transfused when hemoglobin decreases to < 7.0 gm to target a hemoglobin of 7.0-9.0 gm. One adult study[24] strongly recommends Hb >10 gm during 1st 6 hrs of treatment in patients with sepsis. So far pediatrics evidence supports blood transfusion between Hb 5-7 gm/dl.[16]

Risk and benefit is similar in stable critically ill children for Hb 7.0-9.5 gm/dl.[22] There is no need to transfuse if Hb > 9.5 gm/dl.

Transfusion Reactions

Hemolytic Transfusion Reactions

Hemolytic transfusion reactions are the result of antibodies in the recipient's plasma directed against antigens on the donor's erythrocytes. This results in rapid intravascular hemolysis of the donor red blood cells. ABO incompatibility due to clerical error is the most frequent cause. This results in hemoglobinemia, hemoglobinuria, disseminated intravascular coagulation (DIC), renal failure, and complement-mediated cardiovascular collapse.

The recipient's antibodies to Rh or non-ABO antigens cause extravascular hemolytic reactions. These patients usually have been exposed to the antigen through previous pregnancies, transplantation, or transfusions. Antibody titers often are too low to be detected through routine antibody screening, but production of antibodies becomes amplified with re-exposure. These antibodies do not activate complement; therefore, no intravascular hemolysis occurs. Instead, the RBC's are tagged for removal by splenic macrophages.

Nonhemolytic Febrile Reactions

Nonhemolytic febrile reactions have been thought to be due to recipient antibodies formed against donor WBCs or platelets. More recently, these reactions have been postulated to stem from the formation of cytokines during the storage of the blood. These reactions seldom proceed to hypotension or respiratory distress.

Anaphylactic Reactions

Anaphylactic reactions most often are observed in those patients with a hereditary immunoglobulin A (IgA) deficiency. Some of these patients have developed complement-binding anti-IgA antibodies that cause anaphylaxis when exposed to donor IgA.

Proteins in the donor plasma can cause minor allergic reactions. This is an anaphylactoid reaction and is observed more frequently with components containing large amounts of plasma, such as whole blood, pooled platelets, and fresh frozen plasma.

Massive Transfusion Complications

Massive transfusion is defined as the replacement of the entire blood volume within a 24-hour period or the replacement of 10 units of blood over the course of a few hours. Complications of massive transfusion include the following:

- Coagulopathy is caused by a dilutional effect on the host's clotting factors and platelets, as well as the lack of platelets and clotting factors in packed red blood cells.

- Volume overload
- Hypothermia
- Hyperkalemia may be caused by lysis of stored red cells and is increased in irradiated red blood cells.
- Metabolic acidosis and hypokalemia may be caused by the transfusion of a large amount of citrated cells.
- Hypocalcemia due to citrate toxicity may occur in those with hepatic failure, congestive heart failure (CHF), or other low-output states. It is increasingly uncommon with the use of component therapy.

Graft versus host Disease

Transfusion-associated graft-versus-host disease (TA-GVHD) occurs when an immunosuppressed or immunodeficient transfusion recipient receives immunologically competent donor lymphocytes. The transfused histoincompatible T lymphocytes proliferate and engraft in the immunocompromised host, who is incapable of rejecting foreign cells. The degree of similarity between the HLA antigens of the blood donor and the recipient aids in engraftment. Once this occurs, donor lymphocytes proliferate and clinical symptoms begin, usually 4 to 30 days following transfusion. Clinical manifestations include fever, erythematous rash, anorexia, nausea, vomiting, and profuse watery diarrhea. The rash may progress to bullae formation and desquamation. Liver dysfunction, from simple LFT elevations to fulminant hepatic failure, may occur. Severe cytopenias help to differentiate TA-GVHD from that which occurs in bone marrow transplant recipients in TA-GVHD, the bone marrow hematopoietic progenitors are particularly affected. TA-GVHD is fatal in 90 percent of reported cases in children. Diagnosis is usually made postmortem, but may also be accomplished before death with biopsy of skin or GI tract, by identifying chimerism with HLA typing, or by differential typing with RFLP analysis of donor and recipient. Molecular HLA typing may be particularly helpful.

Patient groups at risk for TA-GVHD include bone marrow transplant recipients of any age and infants who undergo either exchange transfusion or simple transfusion in utero followed by transfusion postnatally. Infants with unsuspected congenital immunodeficiency disease, as well as older children with immunodeficiency acquired congenitally or after chemotherapy, may also develop TA-GVHD. No reports of TA-GVHD in HIV infected patients have been published. Some neonatal centers use irradiated blood for all premature infants on the basis of the known cellular and humoral immune dysfunction in these infants, but this practice is not universal. Because TA-GVHD has been reported following use of leukodepleted products, irradiation is currently the only adequate method to prevent TA-GVHD. Both freestanding blood irradiators and radiotherapy units can deliver the necessary dose of 2500 cGy to the midplane of the product/products with a minimum of 1500 cGy to any other area of the bag. This dose will not alter the function of either platelet or white blood cells. However, red blood cells irradiated and then stored overtime have an exaggeration of the storage lesion with markedly elevated plasma potassium (> 75 mmol/L) and poor *in vivo* survival. Because of these findings, irradiated red blood cells can be stored only for 28 days from the date of irradiation.

Transfusion-related Acute Lung Injury

Transfusion-related acute lung injury may be caused by transfusing any plasma-containing blood product. It is caused by the interaction between the recipient's leukocytes and pre-existing donor antileukocyte antibodies, and the infusion of blood storage related lipids. Human leukocyte antigen (HLA) class I, HLA class II, and neutrophil-specific antibodies in the plasma of both blood donors and recipients have been implicated in the pathogenesis of TRALI. This results in complement activation and increased pulmonary vascular permeability. In addition, mediators of inflammation that form while the blood is in storage are also felt to be contributory.

The incidence of TRALI reported is high as 1-2% of the total transfusions. The clinical features of TRALI are:

1. Dyspnea/respiratory distress requiring oxygen support in virtually all the patients.
2. More that 70% of the patients may require ventilatory support
3. Documented hypoxemia in all
4. Hypotension in majority
5. Fever is very common
6. Hypertension is unusual feature

The Canadian Consensus Conference in Toronto in 2004 suggested a definition of TRALI with following features:

1. The occurrence of acute respiratory distress during or within 6 hrs of transfusion.
2. Absence of signs of circulatory overload.
3. Radiographic evidence of bilateral pulmonary infiltrates.
4. Hypoxemia: $PaO_2/ FIO_2 < 300$ or pulse oximetry < 90% on room air or other clinical evidence.
5. No preexisting acute lung injury or presence of risk factors for same.

The patients of TRALI should be managed as per the protocols of the ARDS network study. Lung protective strategies using low tidal volume ventilation with using optimum PEEP should be practiced. Permissive hypercapnia, and maintaining good hemodynamics and organ function is the key to management. The mortality rate in cases of TRALI is relatively low 6-10%. The long term function of the lungs seems to be essentially the same as that for patients who never experience TRALI. There is no apparent late occurrence of fibrosis or other structural damage to the lung parenchyma as a result of TRALI.

Fresh Frozen Plasma[25]

For pediatric and neonatal transfusion practice plasma prepared from a standard unit of blood within six hours of collection can be separated into 2-3 attached satellite bags which are then stored below –20°C as Fresh Frozen Plasma. Before use these bags are thawed under controlled conditions.

Guidelines for Transfusion of Fresh Frozen Plasma

FFP is often requested for intensive care patients with abnormal coagulation rest results, under the twin assumption that these tests predict bleeding risk and that transfusion will reduce that risk. Neither of these assumptions is based on solid experimental evidence. Further more FFP is not indicated to correct hypovolemia or in the setting of a supratherapeutic coumadin effect in the absence of active bleeding. Some of the well described adverse effects of FFP transfusion are allergic reactions, transfusion related acute lung injury and transfusion related circulatory overload.

In patents who are bleeding, and have been massively transfused with washed cell saver RBC's, FFP is used to treat dilutional abnormalities and preventing bleeding complications. But there is no evidence for effectiveness of the prophylactic use of FFP in preventing bleeding at the time of invasive procedures. Also the value of abnormal coagulation test results, prolonged prothrombin time and INR for predicting bleeding complication is very limited and their routine use as the basis for FFP transfusion has been seriously questioned.

In many patients with an abnormal INR, specific factor concentrations remain adequate to prevent microvascular bleeding. And also the standard recommended dose of FFP fails to correct the coagulation deficit in majority of the critically ill patients. IT has been shown that large volumes of FFP result in only transient (2-4 hr) corrections in some coagulation factors in patients with liver disease (Table 74.1).

Numerous studies have shown that invasive procedures can be done safely in patients with mildly abnormal preprocedure laboratory test results by skilled physicians who frequently perform these procedures like central vein cannulation, thoracocentesis, paracentesis and liver biopsy patients. The current practice holds that the FFP transfusion is likely to expose patients to transfusion risks with little or no documented benefit.

So FFP should be reserved for active bleeding attributable to coagulation factor deficiency. Prophylactic use is controversial. FFP should not be used as a plasma expander.

Dose: 10-15 ml/kg body weight.

ABO group specific FFP or AB FFP can be used. No cross-matching is required. It should be transfused within 4 hours of thawing and should not be refrozen.

Platelet Transfusion[25]

Thrombocytopenia is a common problem in the intensive care unit and is associated with adverse outcomes. In the absence of specific contraindications like heparin induced thrombocytopenia and thrombotic thrombocytopenia purpura, platelet transfusions have been used to correct thrombocytopenia in situations where there is active bleeding or an invasive procedure or to prevent spontaneous bleeding in individuals with severe thrombocytopenia (< 10-20000, platelets/dl).

Table 74.1: Fresh frozen plasma (FFP)

Current practice	*Clinical use*	*Evidence*
FFP transfusion indicated	Multiple coagulation factor deficiencies (Liver disease, DIC, dilutional coagulopathy, vit k deficiency, need for a rapid reversal of coumadin anticoagulation) in the setting of active bleeding	No formal studies, expert opinion and anecdotal experience
Controversial	Prior to an invasive procedure (Central line placement, thoracocentesis, paracentesis, Lumbar puncture, endoscopy, interventional radiology procedure)	No evidence for or against
FFP transfusion not required.	Volume replacement To prevent spontaneous bleeding Multiple transfusions in the absence of demonstrated coagulopathy	No evidence for or against No evidence for or against No evidence for or against

In bleeding patients massively transfused with packed RBCs, and crystalloid, platelet transfusions may be indicated to treat dilutional thrombocytopenia. Since children who are critically sick, have normal bone marrow reserve, and can make more platelets in the face of increased demand. In patients with normal marrow function, the risk of bleeding from thrombocytopenia may be lower as has been established for patients with immune thrombocytopenia. Patients with abnormal platelet function or associated coagulation abnormalities would have a higher risk of bleeding for an equivalent degree of thrombocytopenia.

The risks of platelet transfusion include bacterial contamination, allergic febrile reactions, venous thromboembolism, TRALI and TACO. For even critically sick patients a restrictive strategy has been recommended to prevent spontaneous bleeding. Limited data supports the safety for central line placement, thoracocentesis, paracentesis, and liver biopsy in thrombocytopenic patients, but the exact threshold for transfusion has not been defined. In a recent large series, children with thrombocytopenia safely underwent lumbar puncture without platelet transfusion regardless of platelet count (Table 74.2).

Irradiated Blood Components

Indications

Severe immuno-suppressed patients to prevent graft versus host disease (GVHD):

1. Bone marrow transplant patients
2. Peripheral blood progenitor cell transplant patients
3. Pre-mature newborns

Table 74.2: Platelet transfusion

Current practice	*Clinical use*	*Evidence*
Platelet transfusion indicated	Severe thrombocytopenia (Platelet count < 50, 000/dl) in the setting of an active bleeding	No formal studies, expert opinion and anecdotal experience
	To prevent spontaneous bleeding in the setting of very severe thrombocytopenia (Platelet count < 5- 10, 000/dl)	Evidence based
	Severe thrombocytopenia (Platelet count < 50, 000/ dl , prior to an invasive procedure (Surgery, central line placement, thoracocentesis, lumbar Puncture, endoscopy, interventional radiology procedure)	Expert opinion and not evidence based
	To prevent spontaneous bleeding in the setting of moderately severe thrombocytopenia (Platelet count < 10-50,000/dl) in the setting of sepsis, antibiotic use or other coagulation abnormality	Expert opinion, not evidence based

Contd...

Contd...

Current practice	*Clinical use*	*Evidence*
	Platelet dysfunction disorders (Uremia, thromboasthenia, antiplatelet drugs) , in the setting of active bleeding when DDAVP and cryoprecipitate are not effective	NO formal studies, experience and anecdotal reports
Platelet transfusion not indicated	TTP and HIT; use of platelet transfusion is contraindicated by a high risk of thrombotic complications	Evidence based
	Prior to bone marrow biopsy, regardless of the platelet count	Evidence based
	To prevent spontaneous bleeding in moderately severe thrombocytopenia (Platelet count 10-50,000/dl)	Evidence based
	Lumbar Puncture in children unless platelet count < 10,000/dl	Evidence based

4. Patients with hematological malignancies
5. Intrauterine transfusion.

Before sending the request for irradiated blood components consultant incharge of the patient should discuss with the consultant of transfusion medicine department.

Because TA-GVHD has been reported following use of leukodepleted products, irradiation is currently the only adequate method to prevent TA-GVHD. Both freestanding blood irradiators and radiotherapy units can deliver the necessary dose of 2500 cGy to the midplane of the product/products with a minimum of 1500 cGy to any other area of the bag. This dose will not alter the function of either platelet or white blood cells. However, red blood cells irradiated and then stored overtime have an exaggeration of the storage lesion with markedly elevated plasma potassium (> 75 mmol/L) and poor *in vivo* survival. Because of these findings, irradiated red blood cells can be stored only for 28 days from the date of irradiation.

Granulocyte Transfusion

The role of granulocyte transfusion has decreased with better antimicrobial agents and the use of hematopoietic growth factors, e.g., granulocyte and granulocyte-macrophage colony stimulating factors (G-CSF and GM-CSF). However, granulocyte transfusion appears to be effective in gram-negative septicemia in association with an absolute granulocyte count below 500/mm. As with the red cells and platelet transfusion, granulocytes are irradiated prior to infusion in small (immunodeficient) infants to prevent GVHD (graft versus host disease).

Dose: 10-15 ml/kg (1-2 × 109 granulocytes/kg) every 12-24 hrs. Granulocytes are stored at 22 ± 2°C without agitation for 24 hours.

Table 74.3: Composition of cryoprecipitate

Constituents	*Amount*
Factor VIII	80–100 Units/Concentrate
Fibrinogen	150–250 mg/Concentrate
Von-Willebrand Factor	40–70% of original FFP

Cryoprecipitate (Table 74.3)

It is the insoluble portion of plasma remaining after the fresh frozen plasma has been thawed under control conditions.

Indications for Transfusion of Cryoprecipitate:

- Bleeding, or an invasive procedure, in Hemophilia A or von Willebrand's disease.
- Afibrionogenemia—congenital or acquired
- Disseminated Intravascular Coagulation

Dose: 10-15 ml/kg body weight.

Apheresis of Blood Components

Advantages of Apheresed (cell separated) blood component include:

1. Provision of adequate adult dose from single donor.
2. Reduction of donor exposure to the patient, thus improves blood safety.
3. Reduction of bacterial contamination, especially in platelets.
4. Lower chances of refractoriness to blood components.
5. One donor can donate platelets twice a week provided platelets counts are adequate.

Blood Transfusion Practices in Neonates

Blood transfusion requirement in neonates has increased in the recent years because of the advances in the care of premature and sick infants.[26-27]

Transfusion of blood should not be solely based upon the hemoglobin/hematocrit level but also on the clinical assessment of each patient. Blood transfusion requirements in neonates are broadly categorized into two groups: (A) Exchange Transfusion (B) Top-up transfusion.

Whole Blood or Packed Red Cells

The use of whole blood in neonates is primarily for exchange transfusion. In all other circumstances packed red cell transfusion is preferable in neonatal and pediatric age group. The major problem of supplying small volume of blood transfusion in neonates has been solved with the introduction of multiple blood collection packs (quad packs). This has solved the problem of blood wastage and also helps to earmark dedicated unit of blood for frequent transfusion to individual neonate or a child to avoid multiple donor exposure.[28-31] Blood collected in CPD-A or blood collection bags with additive solutions (ADSOL/SAGM) is used for transfusion purposes in neonates. The earlier concept that additive solutions are toxic to immature neonatal kidney have been disproved by several clinical trials and it has been demonstrated that the red cells stored in additive solutions are as safe and effective as CPDA stored red cells.[29] Sterile bag-to-bag connecting devices (docking device) are now available which also help in providing small volumes of red cells/ components to be transferred from large unit to a transfer bag aseptically and without altering the shelf life of blood/blood component. Some neonatologists advocate the use of walking donor program where the required amount of blood is drawn from donor directly in syringe containing appropriate amount of heparin before have been given to the newborn infants.

Volume of RBCs to be Transfused

The volume of packed red cells to be transfused may be calculated as:

WEIGHT IN KG × BLOOD VOLUME PER KG × (DESIRED HEMATOCRIT – OBSERVED HEMATOCRIT)

Hematocrit of the Blood to be Transfused

Generally 10-15 ml/kg of packed red cells are transfused.

PRBCs made leukopoor using third-generation leukodepletion filters should contain < 5 × 1000000 leukocytes per product to prevent febrile nonhemolytic transfusion reactions. Recently published SOAP study has attempted to address the use of leukopoor red blood cells and platelets to decrease alloimmunization, postoperative infection and tumor recurrence, and to obviate post transfusion cytomegalovirus (CMV) infection. In these settings, the goal is to reduce the white blood cell number to < 5 × 1000000.

Exchange Transfusion

1. Mainly neonatal exchange transfusion will be discussed.
2. Exchange transfusion is an effective method for correcting anemia without increasing the probability of circulatory overload, congestive cardiac failure and removing toxic/harmful substances from circulation.

Indications

The main indications of exchange transfusion are:

- Hemolytic disease of newborn (HDN)
- Sickle cell anemia
- It has also been tried in severe malaria for reducing parasitemia.[32-34]

In infants with moderate to severe HDN and exchange transfusion is performed with the following objectives:

- To lower serum bilirubin concentration prevents kernicterus.
- To provide compatible RBC's with adequate oxygen carrying capacity.
- To reduce the amount of incompatible antibody.
- To remove the babies coated RBC, which contribute for additional bilirubin once destroyed.

Criteria for Exchange Transfusion in Rh-HDN

The criteria for exchange transfusion depends upon three main parameters, i.e. cord blood hemoglobin, bilirubin and birth weight (Table 74.4). Accordingly, all newborn at risk must be monitored closely, especially by doing bilirubin estimation at 4-8 hrs intervals with the objective of keeping serum bilirubin level under 20 mg/dl in full term infants and under 15 mg/dl in premature infants. The Table shows parameters for exchange transfusion in HDN.[25]

Table 74.4: Parameters for exchange transfusion in Rh-HDN

Parameter	Observe	Consider exchange	Exchange
At Birth			
Cord Blood			
Hemoglobin	> 14 g/dl	12-14 g/dl	< 12 mg/dl
Serum Bilirubin	< 4 mg/dl	4-5 mg/dl	> 5 mg/dl
After Birth			
Capillary Blood hemoglobin	> 12 g/dl	12 g/dl in first 24 hrs	<12 g/dl and falling
Serum Bilirubin*	< 18 mg/dl	18-20 mg/dl	20 mg/dl in the 48 hrs

**If the bilirubin level rises at a speed indicating that it will reach 20 mg/dl before the child is 48 hrs old.*

Selection of Blood for Exchange Transfusion in Rh-HDN:

1. Blood should be as fresh as possible (48 hrs) but it should not be more than 5 days old for exchange transfusion to ensure long survival of red cells in the infant and to avoid high level of plasma potassium in the transfused blood.
2. Rh (D) negative blood of the same ABO group as that of baby's is used if ABO group of the baby is the same as that of the mother or its compatible with mothers blood (Table 74.5)
3. When baby's ABO group is not compatible with mother's ABO group or if donor's unit is prepared before delivery, it should be O Rh(D) negative blood and it should be free from hemolysins anti-A and anti-B.
4. In case exchange transfusion is required more that once, subsequent blood should be of the same ABO and Rh type as that of the first time.
5. If the mother's antibody is reactive against a high frequency antigen and no compatible blood is available:
   a. The mother's siblings can be tested for compatible blood.
   b. A unit of blood can be collected from the mother, if the obstetrician agrees that is safe. Mother's red cells are constituted in AB plasma.
   c. If no compatible blood is available and the clinical situation is urgent, exchange transfusion with incompatible blood (for the high frequency antigen) is preferred to no transfusion at all as it helps to remove antibody and bilirubin. With holding of blood may result in death of the infant.
6. In areas where sickle cell anemia is prevalent, the donor blood should be screened for sickle cell trait before the blood is used for exchange transfusion.

Table 74.5: Selection of Blood for exchange transfusion in Rh-HDN

Baby's blood	Mother's blood	Blood group for exchange
A	A, AB	A or O
	O, B	O
B	B, AB	B or O
	O, A	O
O	A, O, B	O
AB	A	A or B
	B	B or O
	AB	AB, A, B or O

Volume and Hematocrit of Blood for Exchange Transfusion

Ideally an exchange transfusion equal to twice the newborn infant's blood volume is recommended. The blood volume of a full term newborn is approx 85 ml/kg. Exchange transfusion with partially whole blood. Some clinicians like to exchange relatively large volume of blood, e.g., 200 ml/kg in 60-90 min.

Special consideration in compatibility testing for exchange transfusion

1. If ABO group of mother and the infant are compatible, it is convenient to obtain the serum from mother than from the infant for compatibility test.
2. If mother's blood is not available or the ABO group for mother is not known or the ABO group of mother and infant are incompatible, baby's serum or the elute form cord cell is used for cross-matching.
3. Blood should be cross-matched against mother's serum by IAT and enzyme method.

Newer Directions

Blood Salvage and Autologous Transfusion

The collection and reinfusion of a patient's own blood can decrease the need for homologous blood transfusion. This goal may be accomplished by one or a combination of the following modalities:

a. Preoperative blood donation with subsequent blood bank storage and reinfusion during or following surgery.
b. Acute normovolemic hemodilution, whereby blood is collected immediately preceding or following anesthetic induction and reinfused at the end of the surgical procedure.
c. Intraoperative and postoperative blood salvage, whereby blood shed into the operative field or enclosed space is collected, washed, and reinfused during or after surgery. These procedures have been used frequently in adults and are gaining acceptance in the pediatric population in western countries.

When a pediatric patient is admitted to the ICU following a surgical procedure in which any combination of the above methods has been employed, he is at risk for the development of dilutional coagulopathy. Because these patients are receiving salvaged, washed packed red cells, coagulation factors, as well as platelets, may decrease to levels that place the patient at risk for hemorrhage. Laboratory monitoring of the platelet count, as well as screening coagulation assays, should be used to gauge the need for replacement therapy.

Blood Substitutes

Two prospective randomized studies[35] have examined the use of Recombinant Human Erythropoietin for the management of anemia in critically ill patients in an effort to reduce blood transfusion rates. In the first trial, therapy with rHuEpo was associated with 50% reduction in blood transfusion compared with placebo using a loading dose strategy (300units/kg/daily for 5 days), then every other day till discharge from ICU. The second study reported a 10% reduction in the number of patients receiving any blood transfusion and a 20% reduction in the total number of units transfused using a rHuEpo dosing of 40,000 units weekly. More light will be thrown on the use of rHuEpo, as more trials results are published, and more evidenced is gained in the use of these products.

Similarly two Randomized, placebo controlled , double blind trials (one in blunt trauma and one in penetrating trauma) were conducted simultaneously to evaluate the efficacy and safety of recombinant factor VIIa (rFVIIa), as adjunctive therapy for control of bleeding in patients with severe blunt or penetrating trauma. The trials concluded a significant reduction in RBC transfusion in severe blunt trauma. Similar trends were observed in penetrating trauma. The safety of rFVIIa was established in these trauma population within the investigated dose range (200,100 and 100ug/kg).[36,37]

Over the past 40 years, a number of red blood cell and platelet substitutes have been developed, with few coming to clinical trial. Major classes of blood substitutes currently being researched include: Cross-linked hemoglobin including polyconjugate, tetrameric and recombinant hemoglobin, Lipid membrane encapsulated hemoglobin using liposome and nanocapsule technology, and perfluorochemicals.

Recombinant factors VIII and VIIa are licensed and used for hemophilia A patients and those with inhibitors. Clinical trials are ongoing on the safety and efficiency of recombinant factor IX. To date, there are no platelet substitutes.

SUMMARY

To summarize, the issue of transfusion of any blood component in the Intensive Care area should not be a casual and callous decision, rather it should be critically evaluated. The benefits of such an intervention should be weighed against the risks of transfusion, on an individual basis depending upon the disease status of the child, hemodynamics status, status of oxygen delivery and oxygen consumption, and the need should be individualized patient to patient basis, depending upon the actual physiological needs of the child. The liberal transfusion strategies should be avoided in the intensive care area, and the use of FFP for volume replacement, for correction of deranged coagulation parameters and for protein supplementation should be criticized. Platelets should always be judiciously used as per the recommendation of the critical care guidelines and low platelets without any obvious bleeding should not cause panic and alarm to transfuse the child. Role of Recombinant Human Erythropoietin and Activated factor VII is appearing in the literature, and these products may be a consideration in the given specific case.

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APPENDIX

Leukocyte Reduction of Blood Components

Leukocytes (WBC) are present in varying concentrations in all cellular blood components, including modified whole blood, red blood cells, platelets prepared from units of whole blood, and platelets collected by apheresis. The average unit of red blood cells contains 2.0-5.0 x 10^9 leukocytes, a platelet concentrate from a unit of whole blood contains 0.5-2.5 x 10^8 leukocytes, and some apheresis platelet collections using older technology may contain up to 5.0 x 10^9 leukocytes. As much as a 3 to 4 log reduction of contaminating WBC can now be achieved in both red cell and platelet products using either leukocyte filters or, in the case of single donor platelets, apheresis devices designed to reduce the number of WBC collected, resulting in fewer than 10^6 WBC/product. The FDA permits blood products to be labeled "leukocytes reduced" if they contain less than 5.0 x 10^6 WBC. Depending on the method, leukocyte reduction may be carried out at the Blood Center shortly after or during collection (pre-storage), after storage but before issue from the Blood Center, or at the bedside (post-storage). Although bedside filtration has been shown to be effective, it has drawbacks: for example, as blood warms during transfusion, filtration becomes less efficient. In addition, this process can only be quality-controlled on products at the Blood Center. Therefore, it is Universal Leucocyte reduction is practiced in various countries as USA, Canada, Europe, Japan, Australia to name a few.

Clinical Indications for the Use of Leukocyte-Reduced Blood Components

Established Indications

- *Preventing non-hemolytic febrile transfusion reactions*: Leukoreduction reduces the risk of febrile non-hemolytic reactions through at least two mechanisms. Some febrile reactions are the result of an interaction between patient antibodies and donor leukocytes leading to release of cytokines. Another proposed mechanism is the release of cytokines by recipient cells after interaction with antigen-antibody complexes consisting of donor leukocytes or platelets and patient anti-leukocyte, anti-HLA or anti-platelet antibodies. Contaminating leukocytes cannot always be implicated in the pathogenesis of febrile non-hemolytic transfusion reactions. Febrile reactions occur in some patients without detectable antibodies and also have been reported in individuals who have no history of previous transfusion or pregnancy. Furthermore, febrile reactions to platelets are more likely with platelets that have been stored longer, suggesting that these reactions can be accounted for by cytokines released by white cells during storage of platelet concentrates, which can only be prevented by prestorage leukoreduction.
- *Reducing CMV transmission by cellular blood components*: CMV is an important cause of morbidity and mortality in immuno-compromised patients. Since CMV is a leukotropic virus, leukocyte reduction has received significant attention as a method to reduce the risk of primary CMV infection in certain groups of patients. In clinical trials, leukoreduction prevents transfusion-transmitted CMV infection in low birth weight infants. In bone marrow transplant recipients, it is as effective as CMV-seronegative blood components in preventing CMV transmission.
- *Reducing HLA alloimmunization to platelets in patients and delay in platelet refractoriness:* Platelet survival is frequently diminished in patients who require repeated transfusions. This is most commonly due to antibodies directed against HLA Class I antigens expressed both on white cells and platelets. There is evidence that it is the leukocytes in platelet concentrates, rather than the platelets, which induce the formation of HLA antibodies. Rates of platelet alloimmunization can be reduced if the white cell content of red cells or platelets is less than 5.0 x 10^6/unit. Leukodepletion of this order can be achieved with most of the third generation filters, and also with newer apheresis platelet collection procedures.

Indications Under Review

- *Avoiding transfusion related immunosuppressive effects:* Animal studies as well as infection rates and cancer recurrence in transfused patients suggest an immunosuppressive effect of transfusion. This appears to be mediated by residual white blood cells in blood components and may be abolished by their removal. Several studies, however, have failed to find an independent effect of transfusion. A difficulty with the investigations is that both the number of transfusions given and the risk of cancer recurrence are highly correlated with the extent of the primary tumor. Hence, leucodepletion is helpful in reducing tumor recurrence rates after resection and reducing postoperative wound infections and mortality.
- *Preventing viral reactivation*: Preliminary evidence also suggests that exposure to allogeneic donor leukocytes may reactivate latent viruses. For example, the incidence of CMV infection after transfusion in CMV positive recipients was the same whether blood products were from CMV seropositive or seronegative donors. This suggests that transfusion may reactivate latent CMV infection or that seronegative donors harbor low levels of CMV that is activated following transfusion. In vitro, HIV-infected lymphocytes display viral activation only when cultured with allogeneic leukocytes but not with erythrocytes, platelets or plasma, raising the possibility of HIV activation by transfusion. Hence, leucodepletion is helpful in preventing latent HIV reactivation.
- *Preventing HLA alloimmunization in organ or bone marrow transplant candidates.*
- *Preventing transfusion-associated graft vs. host disease.*
- *Preventing transfusion-related acute lung injury due to passive administration of anti-leukocyte antibody.*
- *Preventing anaphylactic (hypersensitivity) transfusion reactions.*
- *Preventing hemolytic transfusion reactions.*

Section Seven

Pediatric Surgical Issues

CHAPTER 75

Postoperative Care in Pediatric Surgical Patients

Meera Luthra, Praveen Khilnani

Children are frequently admitted to the pediatric intensive care after major surgical procedures. Issues such as major blood loss, major operative stress, tissue dissection, length of surgery, labile preoperative medical status, need for postoperative ventilation, analgesia, fluid and electrolyte management involve the help of pediatric intensivist in postoperative care.

We shall discuss four different categories of patients.

1. Elective Day Care Surgery
2. Thoracic Surgery
3. Abdominal Surgery
4. Surgery for Trauma

Elective Day Care Surgery

Day care surgery such as herniotomy, orchiopexy, circumcision and cystoscopy require good anesthetic management so that the child is awake and pain free after the surgery. An average period of observation preferably with monitoring for 1-2 hrs is usually adequate and the child goes home in the next 2 hrs. Special conditions predisposing to complications such as herniotomy in a low birth weight or preterm baby are at risk because they have apneic episodes. Such babies should be kept in a high dependency unit under very close observation.

Postoperative Care for a Child with Thoracic Surgery

Close monitoring of hemodynamic, respiratory status, oxygen saturations is important. Criteria for elective post-operative ventilation are clinical.

Broadly if intraoperative oxygen requirement is greater than 50 percent, and extensive manipulation of lung has been done, or removal of a major lobe of lung, atelectasis, or major blood loss has occurred, erring on the side of ventilation for at least 24 hours is safer. Adequate analgesia can also be administered without worry of respiratory depression.

Pain relief The ideal and most effective is morphine infusion. Fentanyl is short acting but is equally effective. Besides, adequate analgesia in the form of caudal and epidural used appropriately go a long way in keeping the tachycardia down. Suppositories of paracetamol and diclofenac are now available easily and are excellent in reducing pain. It is important to keep the patient pain free as the subsequent requirement for analgesics is low. If the pain occurs earlier in the postoperative period the requirement for analgesics is higher.

Respiratory Status

Since thoracic surgery is associated with surgery on the lungs and pleura such as pneumonectomy, lobectomy, decortication, esophageal, tracheal abnormalities and mediastinal masses, there is an inherent need to monitor the respiratory status.

Pain in the wound will restrict respiratory excursion and will give a false impression of distress. These are the children who need a very close watch. It is important to note that tachycardia and poor perfusion are the first signs of shock in a child. Obvious causes for shock such as blood loss should be excluded. Even dehydration due to fever or inadequate fluid replacement may be responsible for tachycardia. When tachycardia persists inspite of correction of the above factors there is cause for concern. A fall in blood pressure and irreversible shock can occur. Therefore, these children require to be monitored in the Pediatric Intensive Care Unit (PICU). If the respiratory effort is poor, or tachypnea and retractions are seen oxygen therapy must be begun and an arterial blood gas is done. Most children with such symptoms postoperatively children require ventilation. It is a good idea to keep such patients in the joint care of pediatric intensivists and pediatric surgeons.

The unit must be trained to look after chest tubes, chest bottles, underwater seal and controlled suction units. Besides, the unit must be equipped with nurses trained to look after endotracheal tubes and pediatric drug doses.

All units must be adept at handling central and arterial lines. Strict asepsis can only be maintained if the patient nurse ratio is 1:1 in level III and 2:1 in level II PICU. One of the most important parameter of monitoring is urine output which signifies hydration and perfusion status.

Abdominal Surgery

Basic postoperative care principles apply. Patients after major bowel resection, pull thru operations, pancreas related surgery, hepatobiliary surgery should be routinely admitted to the PICU.

Third spacing (translocation of fluid) is a major problem in first 24-36 hours causing hypovolemia with reduced urine output. This can be easily corrected by infusion of isotonic fluid boluses. Abdominal distension, ileus may also occur. Strict intake and output must be maintained. Drainage of blood and fluid from tubes such as drains, nasogastric tube is recorded. Nasogastric drainage is usually replaced with isotonic fluid such as normal saline or ringers lactate. Blood transfusion is considered if rate of blood loss is fast, immediately requesting surgical reassessment for rexploration. Abdominal distension can result in respiratory distress specially after upper abdominal surgery requiring oxygen therapy with or without assisted ventilation. Narcotic infusion should be carefully monitored for causing respiratory depression and respiratory arrest specially in premature and small infants. Ceftriaxone, amikacin, and metronidazole are a good combination for bowel surgery, specially if gut perforation or intra-abdominal abscess has occurred.

Any surgical patient who has high grade fever following procedures such as cystoscopy in a child with obstructive uropathy should be taken seriously. Sepsis should be thought of immediately and appropriate antibiotics administered after taking into account the local microbial flora. However, in a patient who starts with fever after 48 hours, wound infection should be thought of. It is better to lay open an infected wound and rather than try to treat an obvious abscess with antibiotics. In patients who have received blood transfusion malaria should not be forgotten. Parenteral nutrition should be initiated if enteral feeds cannot be started in 3 to 5 days postoperatively. Finally, fungal infection should be thought of in a child who is on long term antibiotics (about 3 weeks) or TPN without oral feeding. Today fungal infections are treatable yet the mortality is still high.

Surgery for Trauma

Depending upon the site of trauma, i.e. facial, head and neck, chest, abdominal, or extremities requiring orthopedics surgery, admission to PICU is almost always necessary. Physiological principles apply for institution of fluid resuscitation, inotropic and ventilatory support. Most abdominal organ injuries can be treated conservatively with frequent hematocrit and hemodynamic assessments. Chest injuries mostly require pain management and care of pneumothorax, or hemopneumothorax by tube thoracostomy. Mechanical ventilation may be required. Renal injury usually results in hematuria, however bladder and urethral injuries can be serious requiring the expertise of a pediatric urologist, and a nephrologist.

All head injured with poor glasgow coma scores (< 8) patients require PICU care and possible mechanical ventilation with or without neurosurgical intervention.

Extensive bone surgery involving major bones such as femur, pelvis may result in pulmonary fat embolism causing hypoxemia.

Antibiotic therapy following major multiple trauma needs to be individualized based on organ involvement. CSF leaks, otorhea, abdominal perforation, hemopneumothorax, urological injuries require appropriate broad spectrum antibiotic coverage with added anerobic coverage.

SUMMARY

Most patients will do well if postoperative care is carefully planned and executed. Fluid and electrolytes, third spacing, blood loss analgesia and monitoring of respiratory and hemodynamic status remain the major issues. It is safer to keep a postoperative pediatric surgical patient in the PICU for at least first postoperative day. Care of thoracic, kidney and liver transplant, post-cardiac surgery, tracheostomy, thoracoscopy and major airway surgery is discussed elsewhere in this book.

CHAPTER
76

Multiple Trauma: Stabilization and Management in Pediatric Intensive Care Unit

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INTRODUCTION

Trauma in pediatric patient is a preventable disease. Road traffic accidents are the leading cause of death in children and pediatrics. Two-thirds of pediatric major trauma victims have an isolated head injury. Head injury is the most common cause of death due to multiple trauma in pediatric age group. Prehospital trauma care ideally involves a fast response transport system where an emergency medical technician (paramedic), trained in resuscitation and stabilization of the injured child goes to the scene of the accident, and carries out the task of on going trauma care until arrival to the emergency department. In Delhi CATS (Centralized accident and trauma service) has been in place to transport trauma victims to the nearest tertiary care center. Unfortunately due to insufficient state ambulances, lack of trained personnel, traffic congestion and a lack of organized air transport system to transport a trauma victim, this system has a lot of scope for improvement. Private ambulance companies as well as private hospitals are able to provide somewhat more efficient dispatch system as well as trained personnel, however the problem of traffic congestion and lack of availability of many such private transport systems, remains.

Outline of the Chapter

In this chapter, prehospital care of an injured pediatric, including the management at the accident site has been reviewed. Basic principles of initial resuscitation followed by medical management of a pediatric with multiple trauma including a primary survey and a secondary survey for significant injuries will be discussed. Management of specific injuries such as wounds, fractures, head injuries, thoracic and abdominal injuries in the PICU will be reviewed. Finally multidisciplinary team approach in PICU and the surgical management will be briefly discussed. Important key points will be mentioned at the end of discussion.

Prehospital Care of an Injured Child

Main components of prehospital care include

1. Safe evacuation of the injured pediatric from the source of trauma,
2. Quick triage,
3. Airway control and basic CPR,
4. First aid, wound care,
5. Bleeding control,
6. Vascular access,
7. Stabilization of fractures,
8. Pain control,
9. Transport to designated health care facility.

Management at the Accident Site

Quick assessment of the injured child is required

Primary Survey

Primary survey involves a quick survey from head to toe to prioritize management of life threatening issues.

The ABC's of life-saving care are now well-known:

A. Airway assessment and management, with cervical spine immobilization

B. Breathing and provision of essential alveolar ventilation
C. Circulation with prompt control/arrest of hemorrhage
D. Disability, with a rapid neurologic examination
E. exposure of entire child for detection, evaluation and stabilization/treatment of injuries

Basic resuscitation, airway control,cervical spine stabilization, bleeding control and fracture stabilization, openwound dressing, tetanus immunoprophylaxis are required before transport. If bleeding is uncontrolled, intravenous fluids such as normal saline/ringers lactate can be used via intravenous or introsseous route to control hypovolemia and hypotension.

Initial Wound Care

1. Cleaning with saline/savlon/betadine and dressing with antibiotic ointment.
2. Pressure dressing if bleeding(minor arterial bleed will usually stop with pressure). Major arterial bleeder may need to be ligated.
3. All patients should be given tetanus toxoid injection in view of unreliability of immunization status.

First Aid for Fracture

Most fractures can be clinically detected.

Fracture stabilization may involve an arm sling, temporary splint such as figure of eight clavicle bandage or taping of a fractured finger to uninjur finger.

Various sizes of bandages, slings and splints shou be available.

Oral or Injectable non steroidal anti-inflammato agents may be used for pain control in field.

Hospital Management

The discussion will be restricted to initial stabilizatio in the casualty area and specific injuries. A traum score is commonly used by surgeons to classi severity of trauma.[1] Detailed surgical manageme of specific injuries can be obtained in standar trauma textbooks. Tables 76.1 and 76.2 show pediatric trauma score and revised trauma score.

Proper care of the child with multiple traum demands a systematic approach that has bee rehearsed-mentally and physically-so often by al members of the pediatric trauma team that it ha become automatic. This plan includes an under standing of the pediatric airway, control o hemorrhage and principles of resuscitation.[2]

Only following the stabilization of the *child ca an assessment of*, the extent of injuries be undertake and priorities in definitive treatment be established.

Centers which lack this disciplined protocol can provide, on occasion, adequate care to the severely injured child, but the quality of that care will be variable and often below that which is considered state of the art.

Table 76.1: Pediatric trauma score

Point	*+2*	*+1*	*–1*
Size (Kg)	>20	10-20	<10
Airway	Normal	Maintained	Unmaintained
Systolic blood pressure (mm Hg)	90	50-90	<50
CNS	Awake	Obtunded	Coma
Open wound	None	Minor	Major
Skeletal trauma	None	Closed	Open-multiple

Table 76.2: Revised trauma score

Glasgow coma scale	*Systolic blood pressure (mm Hg)*	*Respiratory rate (breaths/min)*	*Points*
13-15	>89	10-29	4
9-12	76-89	>29	3
6-8	50-75	6-9	2
4-5	1-49	1-5	1
3	0	0	0

Following the ABC's, in sequence, comes treatment of the greatest threats to life in the order in which these threats kill.

As an example, airway obstruction is more rapidly fatal than is tension pneumothorax, which is more quickly lethal than shock.[3]

Golden hour.

First hour is considered crucial impacting upon over all prognosis of a child suffering multiple trauma. Resuscitation needs to be started quickly. Time is of essence!

A. Airway

Jaw thrust can be used as airway opening maneuver instead of head tilt and chin lift in patients with possible cervical injury, which should be presumed on all trauma victims.

Foreign matter in the oral cavity, loose teeth, blood, mucus, roadside debris, etc. - can fatally obstruct and is removed best by a finger sweep and large bore suction device.

Blind finger sweep, however, is not recommended as it can push the foreign body deeper into the pharynx.[4]

Oxygen is supplied by the most readily available means. Mouth to mouth resuscitation, or air from a self-inflating bag are acceptable techniques until oxygen by mask is available. A plastic oral airway, placed to hold the tongue forward, is appropriate only if the pediatric child accepts it. Laryngeal mask airway can also be used to assist with bag ventilation.

Should endotracheal intubation be required in emergency situations, this should be performed with a cuffed tube by the oral route as a rapid sequence intubation (RSI). As much as possible sedation and muscle relaxation should be used to perform this with least stress to the patient, avoiding jaw injury, tooth injury, bleeding, laryngospasm, aspiration and raised intracranial pressure.The internal diameter of the tube is age-dependent and, in millimeters, is (4.0 + age in years divided by 4). The distance to which the tube is inserted past the lips, in centimeters, is 11-12 + age in years, though ultimate tube position should always be confirmed by clinical exam (bilateral chest excursions and breath sounds), endtidal CO_2 monitor (if available) and a chest radiograph.

B. Breathing

If the child is breathing , oxygen by mask or nasal cannula may suffice. Mechanical ventilation will be a mainstay of therapy for, most children who suffer severe multiple trauma involving head and/or thorax. A decreased lung compliance can be a major problem, particularly in those patients with extensive thoracic and/or abdominal trauma.

Appropriate ventilation can generally be initiated with an Ambu bag connected to the endotracheal tube. Ventilator rates in the older child can be started at 15 to 20 inspirations per minute.Tidal volume of 8 ml/kg may be selected. There should be adequate chest rise and equal breath sounds on both sides of the chest upon auscultation. Oxygen can be connected via the ambubag.

C. Circulation

After the childs airway is secured and ventilation established, hemodynamic stability becomes the major consideration. In blunt, as well as penetrating trauma, the more common urgent problems are control of ongoing hemorrhage and treatment of shock. Much less common, though equally critical, are cardiac tamponade and cardiac arrest.

Direct pressure applied to bleeding wounds remains the safest method to control external hemorrhage. Torrential hemorrhage from a patients scalp, however, frequently overlies compound or depressed skull fractures with disruption of intracranial veins. Direct pressure on these sites may be impractical.

Elevation of the head several inches above the level of the heart will minimize blood loss.

The clamping of spurting vessels, with hemostats (artery forceps) should generally be avoided, particularly in deep, poorly visualized wounds. Important nerves closely accompany most major arteries, and these may be irreparably damaged by injudicious clamping.

Tourniquets or pressure dressings may be utilized for the temporary control of rapidly bleeding extremity wounds. Blood pressure cuffs are preferable to narrow, make shift tourniquets as they deliver a quantifiable pressure over a broad area. The pressure applied with a tourniquet must exceed systolic blood pressure or it is worse than no tourniquet at all; if too loose, arterial blood is shed and venous blood cannot return to the body.

In any case, any tourniquet should be replaced as quickly as possible with a sterile pressure dressing.

In many areas, tourniquets have been replaced by the pre-hospital application of the military anti-shock trouser (MAST). MAST garment is of particular value in patients with unstable pelvic fractures and/or extensive intra-abdominal injuries. Hemorrhage is reduced and circulation to the heart, lungs and brain is assisted.[4-6]

Shock in the pediatric patient following major injury is practically always due to blood loss. Neurogenic, cardiogenic and septic shock do occur in this setting, but they are rare and precise differentiation is unnecessary initially since initial management differs little, if at all, with that of hypovolemic shock.

Clinically, shock is characterized by tachycardia, cool, pale or mottled extremities, irritability or an obtunded sensorium. Oliguria is a fairly constant finding unless head injury has produced diabetes insipidus. Hypotension is a late manifestation of hypovolemia and may only appear after loss of 25 percent of circulating blood volume due to compensatory mechanisms (primarily release of endogenous catecholamines) present during the early phase of blood loss. A normal blood pressure may fool the clinician into a false sense of security, so meticulous attention to the more subtle manifestations of shock in pediatric patients in general, is essential, such as tachycardia, poor capillary refill, cool extremities, mental status and urine output.

(i) Vascular Access

Vascular access is initially attempted by percutaneous insertion technique at the antecubital vein at the elbow, traditionally the favored sites. An upper extremity catheter is preferred if the potential for serious abdominal injury exists. If patient movement or vasoconstriction makes 2 or 3 attempts unsuccessful, introsseous access should be promptly undertaken. Expertise in this fairly simple maneuver is an essential skill for anyone involved in the care of traumatized children.

The placement of a central venous catheter for the acute fluid resuscitation of a traumatized child can lead to wastage of time. Such catheters are appropriate only subsequently in the pediatric intensive care unit for central venous pressure monitoring.

(ii) Intraosseous Access

Increasing utilization of Intraosseous infusions[7] by pre-hospital personnel has made time consuming vascular access procedures in the emergency department less necessary. Other advantages of this technique include: (i) Many easily accessible routes (tibia, femur, ileum or sternum); (ii) Very little skill is required to perform the procedure, and (iii) The complication rate is exceedingly low. While this modality should be considered for infusion of fluid, blood and most drugs in the initial minutes of resuscitation, conversion to a secure intravenous catheter should be performed when this can be accomplished. This procedure can be used for all ages.

(iii) Choice of Resuscitation Fluid

Debate continues to rage over the ideal initial resuscitation fluid, though most centres utilize Ringer's lactate,normal saline (crystalloids).[7] All patients are given two to three rapid intravenous fluid boluses of 20 ml/kg each. Further management is dictated by the hemodynamic response, or lack of response to this initial infusion. If blood pressure returns to normal, fluid infusion is continued at a maintenance rate. If shock persists after half of the blood volume has been replaced by crystalloid (two to three boluses), blood transfusion is necessary. Usually 10-20 ml/kg of packed red blood cell transfusion is adequate. Ongoing transfusion requirements generally indicate the need for operative intervention.

Secondary Survey

This survey is performed after life threatening injuries have been addressed. Secondary survey involves detection of all injuries.

Following is a discussion of common injuries in an pediatric multiple trauma victim.

Head Injury

Patient with head injury may be brought unconscious, posturing (decerebrate or decorticate), or actively convulsing. All patients should be presumed to be full stomach and oxygen therapy should be initiated. Comatose patients need to be intubated with rapid sequence intubation technique, with due attention to cervical spine stabilization. As mentioned earlier, jaw thrust maneuver can be performed during bag mask ventilation. Head tilt and chin lift maneuvers should be avoided. A cervical spine collar should be placed until cervical spine x rays are obtained to rule out a fracture or dislocation.

Glasgow coma scale (GCS): For clinical evaluation, as much as possible, GCS for adults can be used, however, considering the anatomical, physiological and developmental differences of pediatric age group, a modified GCS is also available for small children (Table 76.3).

Indices of good outcome in head injury

The child has suffered a severe head injury irrespective of child coma score, if any of the following is present:

1. Unequal pupils (a difference of >1 mm)
2. Asymmetric motor examination
3. Open head injury with CSF leak or exposed brain
4. Neurological deterioration (GCS decreased by >2 points)

External Examination

Scalp: subgaleal/subperiosteal haematoma should be looked for

Table 76.3: Modified Glasgow coma scale

Ocular response
4. Pursuit
3. EOM (Extra ocular muscles) intact, reactive pupils
2. Fixed pupils *or* EOM impaired
1. Fixed pupils *and* EOM impaired

Verbal Response
3. Cries
2. Spontaneous Respiration
1. Apneic

Motor Response
4. Flexes and extends
3. Withdraws from painful stimuli
2. Hypertonia
1. Flaccid

Fontanel: To be examined preferably in upright position when child is quiet.

Cranial Suture: Metopic, coronal, lambdoid sutures need to be examined for suture width (normally no palpable gap, except for sagittal suture), for mobility, and overlap (normally no overlap is seen).

Heads Circumference: Any measurement greater than 2.5 cm, above or below normal value for age is abnormal.

Injuries to scalp: These range from abrasion, subgaleal or sub-periosteal hematoma to laceration of various size, shape and depth, depending upon mode and nature of injury. Major lacerations should be sutured as soon as possible, to prevent further blood loss.

Fractures

A. Linear fracture: Single fracture line passes through entire thickness of skull. A simple linear fracture in itself does not require any intervention. Patient should placed in PICU observation specially when the fractures lines are crossing over trajectory of meningeal artery or dural sinus. These inoccuous looking fractures may lead to epidural hematoma and gradual deterioration due to oozing from bone or rapid deterioration when arterial bleeding accumulates or severe bleeding from venous sinus occurs.

   Acute epidural hematoma in contrast to adults is as common in posterior meningeal basal territory as it is from middle meningeal artery.

B. Diastatic fracture: Linear, Comminuted, Stellate Common in children < 3 years

   A diastatic linear fracture is break in skull continuity, more specifically sutures, with coarse definite separation of bone edges by > 5 mm over distance of 2 cm. They are potential source of epidural or subdural haematoma or meningocele.

C. Basilar skull fracture: Basilar skull fracture may present as raccoon eyes (anterior fracture) or battle sign (petechial hemorrhage over mastoid) in middle cranial fossa fracture). Basilar skull fractures may lead to cerebrospinal fluid (CSF) leak or cerebrocele. With CSF leak chances of meningitis are very high and appropriate meningeal coverage with antibiotics (ceftriaxone and vancomycin)should be considered.

D. Depressed skull fracture: Outer table of one or more of the fracture edges lie below normal anatomic level of the inner table as compared to surrounding intact skull. It could be closed or open. An open depressed fracture is surgical emergency.
   Surgery for closed depressed fracture is usually cosmetic but if radiological appearance suggest dural laceration, brain penetration, mass effect, or underlying subdural hematoma, extradural hematoma or Intracranial hematoma exploration required.
   Depressed fracture >5 mm may require surgical intervention.
E. Compound skull fracture: This is a neurosurgical emergency. Once diagnosed clinically, a skull X-ray and CT scan of the head is mandatory. Appropriate management can be undertaken based on findings.

Intracranial Hematoma

Extradural (epidural), subdural, intradural, contusions may be encountered. CT scan of the head is diagnostic and the investigation of choice. Time is of essence.Neurosurgeon must be involved early, and measures to reduce intracranial pressure should be instituted.

Boney Injuries

Following are commonly seen fractures
Hair line/green stick fractures
Clavicle fracture
Humerus fracture
fracture wrist
Spine injury
Femur fracture
Pelvic fracture

Most fractures just require stabilization and pain control. Fracture reduction should not be attempted at the accident site. This should be left for the orthopedic experts in fracture management at the hospital. Major long bone fractures such as femur fracture (shaft) are notorious for unrecognized bleeding enough to cause hypovolemic shock. Fracture of spine, specially unstable cervical spine fractures can be fatal, or may lead to quadriplegia. Spinal cord injury (SCIWORA) without radiological abnormality is common in children only detected classically. Pelvic fractures can involve the urinary bladder or urethra.

Thoracic Injuries[8]

Tension pneumothorax should be emergently treated.

Significant pulmonary parenchymal, cardiac or great vessel injury may result from both penetrating and blunt trauma. In all cases, examination includes inspection of position of trachea, symmetric movement of chest, palpation of fractures and subcutaneous emphysema and auscultation for quality and location of breath sounds.

Lacerations that do not communicate with the pleural cavity are handled in the usual fashion. Externally visible lung constitutes open pneumothorax and is treated with application of partially occlusive dressing and immediate tube thoracotomy.

Rib fractures trigger a progression of pain, splinting, atelectasis and hypoxemia. It is important to prevent this progression through appropriate use of adequate analgesia and pulmonary toilet. Parenteral narcotics, local anesthesia and epidural delivery of narcotics must be considered in appropriate cases. Flail chest arises when >3 ribs are fractured in two or more places gives rise to paradoxical chest wall motion with respiration.

Pulmonary contusion frequently coexists with rib fractures, flail chest and penetrating pulmonary parenchymal injury. Echocardiography is a good test for thoracic trauma to detect hemopericardium tamponade.

Hemothorax arises most commonly from penetrating injuries and requires a chest tube in most circumstances. Retained hemothorax is a significant risk factor for post traumatic emphysema and fibrothorax. For many injuries, thoracostomy is a sufficient surgical intervention. Many guidelines for operative intervention based on the amount of initial drainage and ongoing hemorrage from the chest tube have been proposed. These guidelines should be individualized.

Abdominal Trauma[9]

The abdomen extends from the diaphragm to the pelvic floor. The anterior surface marking of the abdomen therefore extends from the nipples to the inguinal creases. The purpose of secondary survey is to determine whether an abdominal injury has occurred rather than what the abdominal injury is.

Abdominal ultrasonography, (FAST: focussed assessment by sonography in trauma is useful for detecting collection of blood), CT scan and laparoscopy have been proposed as useful adjuncts to evaluate and manage patients with penetrating and blunt abdominal injuries. With the nearly universal utilization of abdominal CT scanning in pediatric trauma[9] patients with potential intra-abdominal injuries, the indications for abdominal paracentesis have been greatly reduced.

Minor blunt hepatic injuries require no therapy. Even major blunt hepatic injuries that are contained within Glissons capsule may be treated expectantly and followed serially. Those with increasing pain or ongoing blood loss may be treated with embolotherapy with laparotomy reserved for patients who fail this modality.

Violation of liver capsule with associated bleeding in blunt hepatic trauma requires surgical intervention. Penetrating injuries should likewise be explored. Management of major hepatic venous or juxta or retrohepatic venacaval injuries, is one of the most challenging issue faced by the trauma surgeon. These patients have exsangiunating hemorrhage requiring placement of atriocaval shunt.

Blunt Splenic injuries can often be managed without surgery especially in children who are hemodynamically stable and injury that can be demonstrated on CT scan. Splenectomy is indicated for progressive clinical deterioration, failing hemotasis or radiologic progression of injury.

Table 76.4 shows grading of splenic and hepatic injuries.

Renal injury: CT scan with contrast will usually pickup renal injury. Grades (see Table 76.5). I to III can be conservatively managed. Grades IV and V with on going hemorrhage, urinary extra vasation, pedical avulsion will need surgical intervention.

Pediatric Intensive Care Unit (PICU) Management Protocol (Flow chart 76.1)

Optimum management is provided by a team approach, necessitated by the multidisciplinarian problems that overlap consistently in pediatric trauma patients. Pediatric intensivists, surgeons and pediatricians must communicate at least daily, and ready access to consultation from other pediatric medical and surgical subspecialists is essential to support any PICU that regularly cares for traumatized infants and children. The PICU nurses should be included in all major discussions. They spend more time with the patient and family than any physician possibly could, and their input on the patient's status and treatment must be actively sought.

PICU Monitoring of a Trauma Patient

Successful management of a pediatric with multiple trauma involves a well planned organized coordinated team effort on the part of critical care transport system personnel, pediatric emergency physician in casualty, pediatric surgeon, pediatric intensivist, pediatric neurosurgeon and many other subspecialists. Pediatric emergency physician should take charge of performing primary survey and initial resuscitation. Pediatric intensivist should take charge of ongoing medical management in the PICU in the preoperative or postoperative period. Pediatric surgeon should take overall charge of investigations to detect various injuries and coordinating surgical repair in order of priority by himself or involving various surgical specialists such as neurosurgeon, cardiothoracic surgeon, plastic surgeon, orthopedic surgeon as deemed necessary.

Frequent clinical examination is the most important human monitoring. Serious injuries can and do escape initial detection, so should always be looked for.

Some of the specific monitoring utilized in the acute care of the traumatized child include, by system:

Cardiovascular

Vital signs
Electrocardiogram (cardiorespiratory monitor)
Noninvasive blood pressure(NIBP)
Continuous arterial blood pressure
Central venous pressure

Table 76.4: Grading system* for hepatic and splenic injuries

Injury	*Grade I*	*Grade II*	*Grade III*	*Grade IV*	*Grade V*	*Grade VI*
Hematoma: Liver, spleen	Subcapsular, <10% surface area	Subcapsular, 10%–50% surface area; intraparenchymal diameter <10 cm (liver) vs. <5 cm (spleen)	Subcapsular, >50% surface area or expanding; ruptured hematoma; parenchymal hematoma; intraparenchymal hematoma >10 cm (liver) vs. >5 cm (spleen) or expanding			
Laceration: liver	Capsular tear < 1 cm parenchymal depth	1-3 cm parenchymal depth, <10 cm in length (liver) vs. not involving a trabecular vessel (spleen)	>3 cm parenchymal depth or involving trabecular vessels (spleen)	Parenchymal disruption of 25-75% of hepatic lobe, or 1-3 segments with a lobe	Parenchymal disruption >75% of hepatic lobe, or > 3 segments within a lobe	
Laceration: spleen				Involvement of hilar vessels with >25% devascularization	Shattered spleen	
Vascular injury: liver					Juxtahepatic venous injuries	Hepatic avulsion
Vascular injury: spleen					Hilar injury with devascularization	

*Advance one grade for multiple injuries, up to grade III.

Adapted from Moore EE, Cogbill TH, Jurkovich GJ, et al. Organ injury scaling: spleen and liver (1994 revision). J Trauma. 1995;38:323-4.

Table 76.5: Grading system* for renal injury

Injury	Grade I	Grade II	Grade III	Grade IV	Grade V
Contusion	Microscopic or gross hematuria, normal urologic studies				
Hematoma	Subcapsular, nonexpanding	Nonexpanding perirenal hematoma confined to renal retroperitoneum			
		<1 cm parenchymal depth (renal cortex) without urinary extravasation	>1 cm parenchymal depth (renal cortex) without urinary extravasation	Extending through renal cortex, medulla and collecting system	Shattered kidney
Vascular injury				Main renal artery or vein injury with contained hemorrhage	Avulsion of renal hilum

*Advance one grade for multiple injuries to the same organ.

Adapted from Moore EE, Shackford SR, Pachter HL, et al. Organ injury scaling: Spleen, liver, and kidney. J Trauma. 1989;29:1664-6

Respiratory

Ventilator alarms
Ventilator graphics
Pulse oximetry
End tidal CO_2 monitoring

Central Nervous system

Glasgow coma scale
Intracranial pressure monitoring
Psychological/mental status evaluation

Coagulation

Clotting parameters
Transfusion requirement

Other systems that demand constant monitoring include:Intake and output, hemoglobin, renal status, metabolic and nutritional status, infection status and dermatologic manifestations of trauma complications.

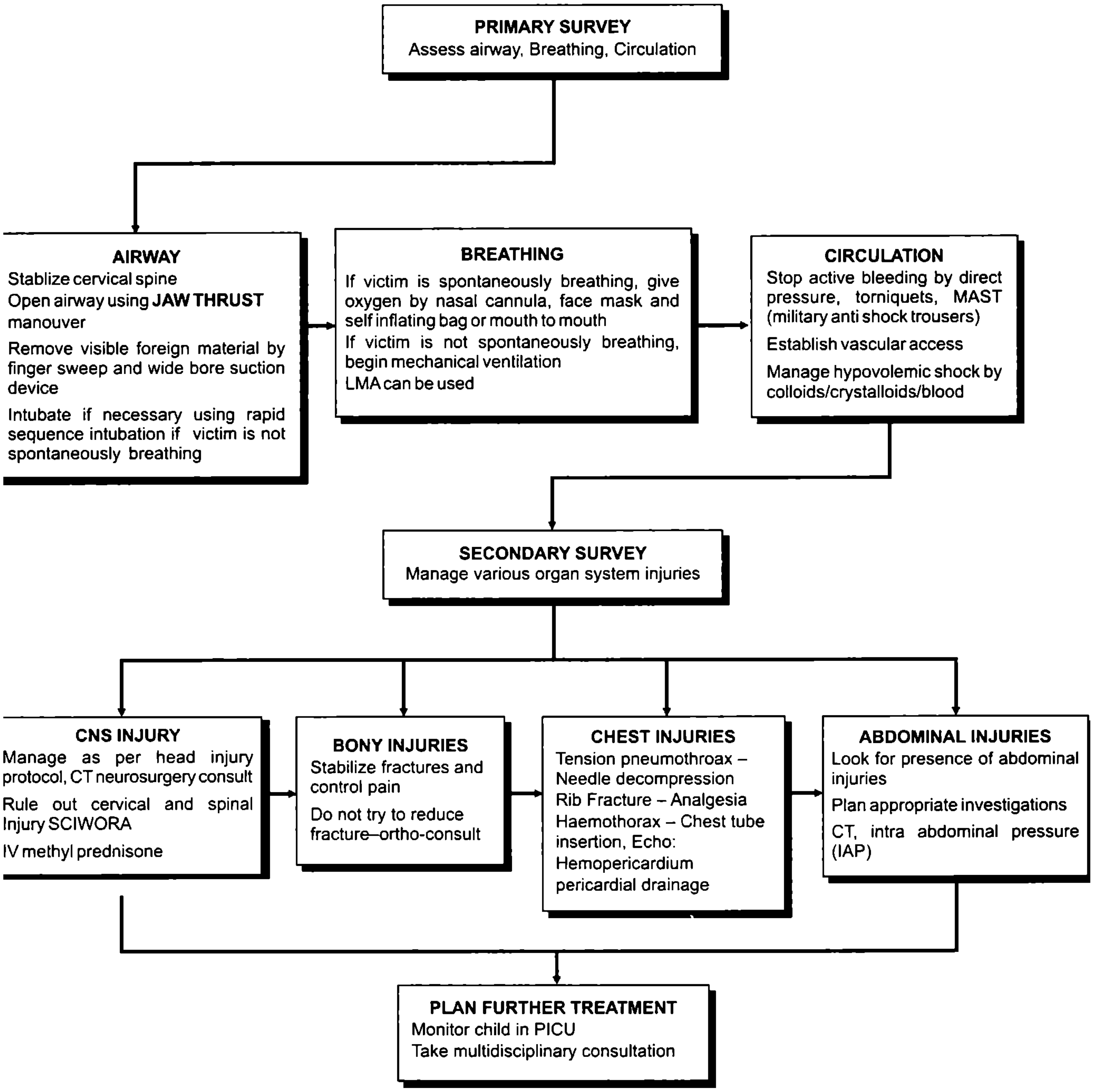
Particular attention to the changes in abdominal girth and intra abdominal pressure (IAP), volume of drainage from chest tubes and other drains, and steep drops in hemoglobin and hematocrit levels is important. A high index of suspicion should be kept for the development of thoraco abdominal abscess, particularly in the context of penetrating trauma and/or postoperative patients.

Though children and pediatrics are most impressive in their recuperative powers, the recovery of a child with massive trauma tends to be slow and gradual, while deterioration may be abrupt and rapid anticipation of the potential complications with any given injury, readiness for any unsuspected sequelae or previously unrecognized diagnosis, and a willingness to continually reassess the patient and his or her progress must accompany our increasing reliance upon (and fascination with) machines and tests that interface intimately with the small child.

Key points

1. Quick transport to the nearest medical facility is the key for survival
2. First aid at the accident site is crucial: **Golden hour (Ist hour)** is important.
   A quick primary survey and prompt institution of resuscitation (airway control,breathing and circulation) and bleeding control must be started.
3. Cervical spine should be stabilized at all times
4. Appropriate Emergency and Intensive care management before the operative intervention is crucial.
5. Trauma must be managed as a team.
6. After initial resuscitation and bleeding control,Injuries detected on secondary survey need on going monitoring and require appropriate medical or surgical management.

Flow chart 76.1: Pediatric multiple trauma


PRIMARY SURVEY
Assess airway, Breathing, Circulation
AIRWAY
Stablize cervical spine
Open airway using JAW THRUST manouver
Remove visible foreign material by finger sweep and wide bore suction device
Intubate if necessary using rapid sequence intubation if victim is not spontaneously breathing
BREATHING
If victim is spontaneously breathing, give oxygen by nasal cannula, face mask and self inflating bag or mouth to mouth
If victim is not spontaneously breathing, begin mechanical ventilation
LMA can be used
CIRCULATION
Stop active bleeding by direct pressure, torniquets, MAST (military anti shock trousers)
Establish vascular access
Manage hypovolemic shock by colloids/crystalloids/blood
SECONDARY SURVEY
Manage various organ system injuries
CNS INJURY
Manage as per head injury protocol, CT neurosurgery consult
Rule out cervical and spinal Injury SCIWORA
IV methyl prednisone
BONY INJURIES
Stabilize fractures and control pain
Do not try to reduce fracture–ortho-consult
CHEST INJURIES
Tension pneumothroax – Needle decompression
Rib Fracture – Analgesia
Haemothorax – Chest tube insertion, Echo: Hemopericardium pericardial drainage
ABDOMINAL INJURIES
Look for presence of abdominal injuries
Plan appropriate investigations
CT, intra abdominal pressure (IAP)
PLAN FURTHER TREATMENT
Monitor child in PICU
Take multidisciplinary consultation

IAP	: Intra-abdominal pressure
LMA	: Laryngeal mask airway
Echo	: Echocardiogram
SCIWORA	: Spinal cord injury without radiological abnormality
FAST	: Focussed abdominal sonography for trauma
CT	: Computerized axial tomogram

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CHAPTER

77

Child Abuse and Shake Injuries

Praveen Khilnani

Child abuse has existed and exists today in all cultures. Historically, defining a given behavior as abusive or harmful varies both between and within cultures as well as overtime. At various times in many cultures the father was the absolute head of the house, with the right to exercise life and death decisions over his property (i.e., his children). Given this right, children were deliberately exposed or killed if they were deformed, illegitimate, or simply not hardy enough to raise. Female infants were often consi-dered a family burden and were similarly discarded. For centuries, children were deliberately mutilated to increase their earnings as beggars; young boys were castrated for harem service or to preserve their high-pitched voices for choirs; and children were sacrificed to the gods for the greater good of the whole community.

Between 1925 and 1946 Dr John Caffey, a pediatrician by training and a leading pediatric radiologist, recognized that multiple fractures were due to trauma. His 1946 publication associating multiple fractures with subdural hematomas raised the question of parents causing the injuries, either covertly or overtly. Over the following years more articles in the medical literature drew the same conclusions, until Dr C Henry Kempe and colleagues, at a conference in 1961 and in an article in 1962, publicly coined the term "battered-child syndrome".

DEFINITION AND ETIOLOGY

The broadest possible definition for child abuse and neglect would include any behavior, whether overt or covert, on the part of a child's caregiver that interferes or might interfere with that child's normal growth and development physically, mentally, or emotionally. This definition allows for the potential of future injury based on past or present incidents and for a broader spectrum of harmful behaviors such as:

- Physical abuse
- Emotional abuse
- Sexual abuse
- Intentional drugging
- Educational deprivation
- Physical neglect
- Nutritional neglect
- Medical care neglect
- Lack of supervision
- Abandonment

Factors frequently cited in the abusers are feeling of isolation, an inability to trust others, and low self-esteem. Environmental factors such as unemployment, poverty, and poor housing overstress an already stressed family. Child factors such as prematurity, developmental delay, disability, temperament, prolonged illness, and illegitimacy can mark the child as "different " and unable to fit into the parents' expected family picture. Approximately 10 percent of abusive care givers are psychotic or sociopathic.

DIAGNOSIS

The first step in diagnosing child abuse is to suspect it. The description of the events surrounding the injury must be as detailed as possible and include a complete developmental history and specific timing

Table 77.1: Histories offered in abuse cases

- No explanation given
- Inconsistent with injury
- Self-inflicted
- Caused by sibling
- Delay in seeking care
- Partial confession
- Varying or discrepant

Table 77.2: Dating of bruises

Age of bruises	*Appearance*
0-2 days	Swollen, tender
0-5 days	Red, blue, purple
5-7 days	Green
7-10 days	Yellow
10-14 days	Brown
2-4 weeks	Cleared

of symptoms and events leading to the admission. Some histories are diagnostic or at least highly suspect for non-accidental injury (Table 77.1).

An inconsistent history is most frequent. Minor falls are blamed for causing complex skull or long-bone fractures, multiple or closed head injury.

Other diagnostic features include a recent family crisis. The social history may reveal a recent family crisis such as unemployment, eviction separation or divorce.

EXAMINATION

All details of the physical examination must be thoroughly documented. CNS trauma, fractures, extensive bruising, and scalds in infants and toddlers and injuries to the buttocks, lower back, genitalia, inner thighs, earlobes, neck and oral cavity at all ages should be considered nonaccidental until proved otherwise. However, the absence of marks, bruises or fractures never rules out child abuse. Children with severe head and intra-abdominal injuries often have no visible external trauma or cutaneous lesions. External injuries are best documented by drawing on a body diagram to be precise.

Estimating the age of external bruises and other injuries can document recurrent abuse. Although the rate of healing varies by age, body area, skin thickness, depth of injury, subcutaneous fat blood supply and other factors, bruises show specific color changes over time (Table 77.2). Healing commences at the periphery and progresses centrally; therefore, the color at the margin is used to approximate the age of the bruise. Bruises and burns are the two most common external signs of physical child abuse or neglect (Table 77.3). Patterned bruises do not usually occur accidentally and must be identified in the record as well as possible. Multiple or severe bruises, particulary on soft tissue areas, are always suspect.

Shake Injuries

This type of injury usually occurs in child less than 1 year of age, and the precipitating event is usually the child's uncontrollable crying. The adult's response is usually one of the frustration, and it appears quite likely that in the majority of the cases the adult does not deliberately plan to injure the child. A sudden loss of control apparently is responsible for this type of trauma.

Recent studies strongly indicate that shaking alone cannot cause the life-threatening brain swelling, subdural hematoma, and brain injury that occur in these children. Frequently the child is tossed into the crib, onto a couch, or occasionally deliberately against a wall or floor. There is usually an impact associated with the deceleration injury that produces the typical picture of "the shaken baby syndrome" and that this term should be changed to be "the shaken, impacted baby syndrome".

Examination

Retina

If history is not appropriate for the child's condition, an integral part of the physical examination, before any other intervention, is a retinal examination for retinal hemorrage. The examination must be complete and thorough. An ophthalmologist should be consulted.

Head

When head trauma is suspected, the head should be carefully palpated and inspected for evidence of bruises, lacerations, hematomas and fractures.

The ears should be examined, as should the mouth. Oral injuries are now recognized as evidence

Table 77.3: General characteristics of accidental vs nonaccidental trauma

Trauma	*Accidental*	*Nonaccidental*
Bruises	Few other than on shins in toddlers	Frequently multiple
	Rounded, nondescript	Often patterned or multishaped
	Over bony prominence	Same, plus soft tissue areas
	Location: shin, lower arms, iliac crest, chin, forehead	Location: trunk, upper anterior and inner thigh, back, buttocks, upper arms, chest, face, abdomen
Immersion burns	Asymmetric	Symmetric
	Often blurred	Clear distinct margins
	Irregular splash marks	None or few
	Few spared areas	Patterned, intertrigonous sparing
	Partial thickness	Full thickness
	Location: random, consistent with history	Location: stocking or glovepattern, lower leg buttocks perineum
	Cause: consistent	Cause: unknown: self-or sibling-inflicted
Spill burns	Irregular margins	Same
	Face, arm, upper trunk, usually anterior	Same; multiple random areas if thrown
	Pattern: consistent With child's position	Pattern: inconsistent
Contact burns	Superficial or partial thickness	Deep or full thickness
	Small area of contact	Full contact area
	Blurred or no pattern	Clear pattern and margins
	Deeper at one edge	Uniform depth
	Exposed areas	Same but not limited
Skull fractures	Unilateral	Same or bilateral
	One bone	Same or multiple
	Single simple linear	Same or multiple, complex, depressed, diastatic
	Narrow (1-2 mm)	Same or wide, especially > 5 mm
	Falls of 3-5 feet	Forceful blunt trauma
	No cerebral injury	Often associated with cerebral, injury or hemorrhage.

of abuse and may include hematomas and laceration to the buccal mucosa and the tongue tears of the frenulum, or avulsion of the teeth.

The pharynx may show evidence of sexually transmitted diseases or acute laceration or abrasions.

The examination of the chest and abdomen should be supplemented by appropriate radiologic investigations such as X-rays and CT (Computerized Tomographic) scans to exclude injuries to lung, liver, spleen, pancreas or duodenal hematoma.

The genitals deserve special attention, even if sexual abuse is not initially suspected. In boys, the external genitals should be examined for evidence of trauma and sexually transmitted diseases. Female genitals should be assessed for the size and shape of the vaginal introitus, the condition of the hymen and evidence of trauma to the perineum, and to the vulva in particular. If at all possible, it is best to perform this evaluation without the presence of a foley catheter. The anus and rectum should be inspected for evidence of trauma, and any laxity of the anal sphincters should be noted.

The skin and soft tissues require a thorough exami-nation, which should be repeated at regular intervals during the first few days to document the appearance and resolution of any bruises and hematomas that may not be clearly visible on admission.

Initial Stabilization

Early care of the airway control of seizures and preservation of adequate ventilation come first. If the baby is flaccid or exhibits abnormal posturing(either extensor or flexor), and is exhibiting a full and tense fontanelle, emergency bilateral subdural taps are done. They often allow drainage of 5 to 15 ml of bloody cerebrospinal fluid bilaterally, and this drainage may frequently result in improvement of the neurologic condition and breathing.

CT Scan of Head

Once the baby is stable a CT scan must be obtained. If the child is irritable it is better to do the scan under general anesthesia with endotracheal intubation than to sedate him with oral or intravenous medication; the hypercarbia and hypoxemia that could accompany sedation with hypoventilation could cause further increases in intracranial pressure (ICP) and a marked deterioration in the patient condition. Rarely will the CT scan demonstrate any significant mass lesion. The most common pattern is that of a posterior triangular shaped interhemispheric collection of blood although the incidence of small to a large subdural hematomas vatries from series to series, more extensive subdural hematomas can occur. Sub- arachnoid hemorrhage is frequently present. The most ominous and often overlooked of the CT findings is that of loss of the gray matter/white matter density difference, with or wothout brain swelling. This pattern is the result of transient or persistent cerebral ischemia and is usually followed by increases in ICP that may be immediate or delayed over 24 to 48 hours and frequently accompanied by seizures. Thus, this pattern on the CT scan should warn the physician of the potential need for ICP monitoring and PICU care despite a neurologic examination that may appear fairly satisfactory.The importance of this finding of low density throghout the hemispheres is that there will almost certainly be a progressive loss of brain tissue, resulting in cerebral atrophy.

Treatment

No specific therapies exist for shake injuries other than in those children with increased ICP. Severely elevated ICP can occur in children with open fontanelles and ICP monitoring is safe in this age group. Hyperventilation, strict control of seizures, osmotic agents, and barbiturates may all be necessary to control the ICP in this group of children. A great deal of the cerebral damage in children who are shaken and impacted apparently is caused, by hypoxia and ischemia, and if the ICP is >20 mmHg the out look for good recovery is very poor; an outcome similar to that for near-drowing patients. Because there is both traumatic and ischemic pathology, the efforts to control ICP are occasionally effective, and the outcome is better than expected, justifying the initial effort. In children with loss of gray matter/white matter density differential, the cerebellum or basal ganglia may appear to be of high density. They are, in fact, of normal density, the remainder of the brain being severely ischemic, and in this group of children the ICP and systemic arterial blood pressure are frequently equal when measured and confirm brain death.

HEAD INJURIES

The child's scalp must be palpated for soft tissue swelling and must be examined for bruises. However, even after they receive a direct impact, skull fractures and externally visible scalp bruises are found in only 50 percent or less. Blunt trauma from an open or closed hand, impact against the wall, floor, or other hard object, and rapid acceleration and deceleration cause the majority of nonaccidental injuries.

Associated unilateral or generalized cerebral edema is the most life-threatening consequence of inflicted head injury. Subdural hematomas originate from tearing of the bridging veins between the brain surface and the dural sinuses and are commonly associated with cerebral edema. In children less than 1 year of age the onset of symptoms is generally immediate or within minutes of non-accidental trauma. Considerable force is needed to produce a subdural bleed in the normal child, making the usual history of falling out of bed or from a table untenable. A large percentage of the children develop obstructive hydrocephalus or cerebral atrophy requiring a shunt operation. Retinal hemorrhage often occurs in association with subdural hematomas or markedly increased ICP, yet it is uncommon in all but the most severe accidental head injuries. If it is noted, ophthalmologic consultation is waranted. Despite the frequency of facial bruises and trauma in abused children, injury to the facial bones is rare. When present, the mandible or orbital regions are usually involved. If traumatic alopecia has occurred recently, the child may have petechial hemorrhage at his hair roots, swelling, and tenderness. The remaining hair is not easily extracted, and the pattern of hair loss is diffuse, in contrast to that with alopecia areata.

ABDOMINAL INJURIES

Severe intra-abdominal injuries can occur without obvious external injury or bruising. Nonaccidental injuries are frequently caused by blunt trauma from a punch or kick or by rapid deceleration from the child being thrown. Plausible explanations are more frequent with these injuries, although simple falls and falls down stairs are inconsistent with the trauma. In many cases the history of abuse comes from the child's talking to hospital personnel when no family members are present.

Abdominal wall tenderness may mask more serious internal trauma or peritonitis. Symptoms may be vague and misleading, and the history rarely mentions direct trauma.

LABORATORY AND DIAGNOSTIC IMAGING STUDIES

The establishment of a suspicion of physical abuse is based on a constellation of data gathered through history taking and physical examination. Clinical laboratory and diagnostic imaging studies are useful in confirming injuries and in ruling out other medical causes that could be associated with the physical findings.

Laboratory Evaluation

Hematological If skin lesions such as petechiae, bruises and ecchymoses of different ages and sizes, and abrasions are present, hemorrhagic diseases (pancytopenias and leukemia) can be excluded by obtaining a complete blood count and coagulation profile, which includes prothrombin time, partial thromboplastin time, platelet count, bleeding time, and fibrinogen and fibrin split products determinations. The last two may be optional.

Biochemical

Serum electrolyte, glucose, amylase, blood urea nitrogen, and creatinine determinations may be useful if blunt abdominal trauma is suspected because of palpable abdominal masses or tenderness, hematuria, or lower rib fractures. When a child presents with severe failure to thrive, intensive care management may include hematologic tests and blood chemistry studies, as well as total protein and albumin determinations. The latter two values will confirm chronic and acute malnutrition.

Toxicological

In addition to the previously mentioned blood studies, liver function and toxicology studies will help elucidate the cause of changes in mental status and acute neurologic deterioration.

Urinalysis

Urine should be collected for urinalysis to screen for renal trauma, and urine toxicology screens can be used to assess exposure to enviornmental products, prescription drugs, and illegal substances in children who present with abnormal neurologic signs or seizures. All abnormal screening tests should be duly confirmed.

DIAGNOSTIC IMAGING EVALUATION

Imaging studies are strongly indicated in infants and young children with evidence of physical injury. These studies may reveal evidence of abuse in a child who is initially evaluated for a suspected natural illness or medical emergency.

Skeletal Survey

The radiographic skeletal survey is the method of choice for skeletal imaging in cases of suspected abuse in children 2 years of age or younger. Patients older than 2 years but less than 5 years of age must be assessed carefully and individually based on clinical indicators of abuse. At any age, however, when clinical findings point to specific injuries suggestive of abuse or nonaccidental trauma, a skeletal survey is useful in the evaluation of occult injuries that may be old or new. The skeletal survey must include:

Anterior and posterior views of the long bones of both upper and lower extremities, as well as the feet, hands, pelvis, and skull. Lateral views of the skull and axial skeleton are required components of the survey.

Radiologic findings may confirm patterns of injury associated with abuse such as metaphyseal lesions, scapular fractures, other injuries that are specific for abuse such as multiple new old fractures.

Long bone X-ray studies are helpful in infants suffering from failure to thrive in order to exclude rickets and osteopenia.

CT Scan and MRI

CT is an important imaging study that is useful in assessing children with blunt or penetrating trauma to the chest or abdomen. The evaluation of pancreatic injury and duodenal hematoma, which are two characteristic findings associated with nonaccidental injury, is helped by CT. Children and infants with signs and symptoms of intracranial injury must have cranial CT or magnetic resonance imaging (MRI) studies, or both. The presence of intracranial hemorrhage, cerebral contusion, edema or infarct without major explainable trauma is highly suspicious and usually diagnostic of nonaccidental injury. CT is a satisfactory imaging modality for evaluating head injuries and seems to detect subarachnoid hemorrhages better than does MRI. However, some investigators indicate that MRI provides better characterization of the age of the blood in areas of the brain. Furthermore, MRI is very good for depicting subdural hematomas over convexities, cortical contusion, and white matter injuries. MRI is recommended for patients suspected of having intracranial injury when clinical findings are not explained adequately by CT.

Ultrasonography

Ultrasonography may be used to evaluate a patient with lesser signs of acute trauma or a constellation of nonspecific abdominal signs and symptoms without explanation. Ultrasonography produces reasonable studies of pancreatic injury, occult duodenal hematoma, or renal injury.

MANAGEMENT

The physician is responsible for both medical manage-ment of child abuse and reporting to authorities. Medicial management is essentially dependent upon the system involved and extent of injury. A detailed discussion regarding the treatment of each of the nonaccidental injury is beyond the scope of this chapter.

LEGAL IMPLICATIONS

Laws of the Indian Penal Code will apply to each specific case. It is the physician's responsibility to suspect child abuse and report to appropriate authorities. It is also important to be nonconfrontational with the parents. It is important for the physician not to accuse the suspect directly even though the history may be strongly suggestive to avoid a possible violent reaction. However, it is important to have evidence such as documentation of physical findings, radiographs, CT scan, laboratory results as well as photographs of the bruises, abrasions and bruises, etc. for later depostion in court.

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CHAPTER

78

Pediatric Anesthesia—for the Pediatrician

S Ramesh

Administering anesthetic agents to babies and small children is not the same as anesthetizing adults. Special training, techniques, vigilance, equipment and approach are required.

It is essential that pediatric anesthesiologists have thorough training and experience in pediatrics and neonatology. They should comfort not only their patients, but also the equally anxious parents, grand parents and host of relatives!

Among the advances in medicine during the past 150 years certainly the introduction of Surgical anesthesia must rank with immunization, antibiotics, asepsis, modern surgery as the profession's greatest gifts to human kind, especially to children. Earlier the anesthesiologist was expected to provide safe anesthesia for children who were undergoing relatively undemanding surgical procedures. With growing ambitions of the surgeons to undertake radical and complicated procedures in more sick infants, the anesthesiologists too had to sharpen their skills and devise appropriate techniques to meet the surgical challenges. As a result, difficult and demanding procedures are now being performed on all age groups of children.

The Pediatric Anesthesiologist Is There a Need for Formal Recognition?

There is increasing evidence that involvement of pediatric anesthesiologists in the peri-operative care of infants and children can positively impact the outcome. Over the past several years, it has become more difficult to define the attributes that make a pediatric anesthesiologist. There is increasing evidence to support the notion that sub-specialists do make a difference in overall morbidity and mortality of infants and children undergoing surgery, either elective or emergency. In an prospective study done by British medical community to identify peri-operative deaths, fifty percent of noncardiac surgical deaths had been cases anesthetized by practitioners who cared for less than fifty infants a year. Several deaths took place in non-specialty settings (i.e. non-children's hospitals) in which no effort was made to provide specialty care for the pediatric patient. More pointedly, in the overall recommendations and conclusions of the report, it is noted that anesthesiologists should not undertake occasional pediatric practice and consultants who take the responsibility for care of children must keep upto date and competent in the management, consider transferring these patients to a facility where necessary support is available. In the long run, not only is this best for your patient, but is also the most cost effective medicine.

Anesthetic Triad

- Sedation
- Anxiolysis
- Analgesia

These are the three main components of Anesthesia. In modern anesthetic practice, we use individual drugs to achieve each one of them, depending upon the type of surgical procedure. This type of Anesthesia is termed as "Balanced Anesthesia". To these original components, two more have been added, i.e. "Awareness" and "Amnesia".

Anesthesia and the Aircraft

Dynamism, time pressure, complexity, uncertainty and risk are seen in such activities as aviation. Aviation offers considerable parallels with anesthesia.

Anesthesia	*Aircraft*
Induction	Take off
Maintenance	Cruising
Recovery	Landing

Fitness for Anesthesia-WHO Decides ?

The choice of the anesthetic technique and judgment on a child's fitness for anesthesia must always be the responsibility of the anesthesiologist to the child. Many times Surgeon asks the cardiologists, pediatricians and other medical colleagues to comment on 'fitness' of a child for anesthesia. In our view, it is inappropriate for other medical colleagues to opine on a child's fitness for anesthesia by 'clearing' or 'giving OK' for anesthesia. We are always grateful for the opinions of our medical colleagues about the diagnosis and the medical status of patients presenting for operation and their current medical therapy, especially when the patient has heart or lung disease.

Is There a Term Fitness for Anesthesia ?

In our view, there is no such term as 'fitness for Anesthesia'. Nobody however, healthy they are, is fit for Anesthesia. That is, everyone who is to be anesthetised has some grade of risks. So to explain the risk to the patients or parents of the child the American Society of Anesthesiologist (ASA) classified various risks factors into VI groups.

ASA Classification

ASA I : No underlying physical or metabolic disturbances.
Example: Good general health in 2-years-old child who will undergo herniotomy.

ASA II : Mild to moderate disturbances that do not interfere with daily routines. Many anesthesiologists include extremes of age (< 1 year or > 70 years) in this category.
Example: Anemia, mild renal insufficiency, asymptomatic heart disease, moderate obesity, well-controlled asthma.

ASA III : Severe disturbances that interfere with ordinary daily activities
Examples: Chronic lung disease, tetralogy of Fallot, insulin-dependent diabetes, severe and compromising physical abnormalities such as Pierre Robin Syndrome or Morbid obesity.

ASA IV : Severe disturbances that are a constant threat to life.
Examples: Extreme prematurity, intractable congestive heart failure, advanced renal, pulmonary, or endocrine dysfunction, critical airway obstruction such as epiglottitis.

ASA V : Moribund condition in patient who is likely to succumb within 24 hours, whether or not an operation is undertaken. Surgery is attempted as a last-hope effort to prevent death and is usually part of the ongoing resuscitation.
Examples: Major trauma requiring continuing cardiopulmonary resuscitation; severe head injury with rapidly deteriorating central nervous system status.

ASA VI : Organ Donor
Physical status classification appended with an E when surgery is undertaken as an emergency–an acknowledgment of additional physical risk factors associated with absence of preoperative stabilization, fasting, or evaluation.
Example: Otherwise good health in a child with testicular torsion, classified.

TRIAD OF ANESTHETIC RISK

So the risk benefit judgment on a procedure should be made before anesthetising the patient for surgery.

Are there Terms 'Mild Anesthesia' or 'Short General Anesthesia (GA)'?

There are no such terms. It is a misconception. There are only two terms *Anesthesia* or *No Anesthesia.* Because whatever may be the duration of minor surgical procedure, there are no short cuts to anesthetic practice. All the steps of Anesthesia such as Pre-Anesthetic Assessment, Induction, Maintenance, Recovery and Postoperative care should go through for each and every surgical procedure.

How Long Should the Child Fast ?

The need for prolonged period of fasting [e.g. NPO (nil per oral/NBM) (nil by mouth) after midnight] before anesthesia induction in otherwise healthy children has been recently questioned. Studies have shown that children who are allowed to drink clear fluids until 2-3 hrs of anesthesia induction do not manifest increase in gastric volume or acidity over those who fast overnight. Accordingly most pediatric anesthesiologists have now liberalized NPO requirements for the patients. Solid food, which includes milk is still not allowed upto 6 hours preoperatively. Children may drink *clear* fluids (upto 10 ml/kg) until 3 hours of the posted surgical time. It is important to note that these guidelines apply to *clear liquids* only (not solids) in otherwise healthy children. Possible benefits of shorter fasting times include minimizing thirst and discomfort while awaiting surgery, less hypovolemic-induced as physical status ASA I E. hypotension during induction and less chances of hypoglycemia.

What Monitoring is Commonly Employed in Routine Pediatric Anesthetic Practice?

A. Pulse oximetry.
B. Noninvasive Blood pressure.
C. Temperature

Introduction of Pulse oximeter to monitor oxygen saturation noninvasively is a great boom in pediatric anesthesia. The pulse oximeter gives both heart rate and oxygen saturation which are the most important vital signs to be monitored in children. Since many of us are aware that most of the problems in children are related to respiratory and airway problems, the pulse oximeter is a very good monitor to warn us before any major catastrophe occurs. We feel that most of the healthy children coming for routine surgical procedure, the blood pressure is a very good indicator of the volume status of the cardiovascular system. The fluid administration can be very well adjusted according to the noninvasive blood pressure monitoring.

The temperature monitoring is very important during pediatric anesthesia and it is mandatory during neonatal anesthesia and prolonged surgical procedures. The neonates and small infants are prone for hypothermia due to various reasons such as large surface area, very little subcutaneous fat and devoid of shivering thermogenesis mechanism. It is vital to not only to monitor temperature but also keep the child warm with various methods. The infusing fluids can be warmed, and the child can be kept warm with the help of warming blankets.

Common pediatric Problems Faced by the Pediatric Anesthesiologist

Upper respiratory infection (URI)-common cold-running nose

Why are we worried of URI?

- May become Lower Respiratory Infection (LRI)
- Incidence of Bronchospasm and Laryngospasm more
- Desaturation is faster.

So elective surgery to be postponed if:

- Fever
- Definite parent's history
- Yellow discharge or crusts
- To wait for at least two weeks after completion of treatment.

In emergency

- Risks to be explained to the parents.
- Modify the anesthetic technique.

Asthma

Asthma is one of the most common and potentially most frightening disease the anesthesiologist must deal with children.

Why are we worried of Asthmatic (wheezing) children?

- Intra-operative bronchospasm
    - Hypoxia
    - Hypercarbia
    - Arrhythmias

So Asthmatic children are grouped into three Groups.

Group I : Wheezy child, no wheezes, no drugs at present

- Surgery in summer if possible.
- Premedication with bronchodilators

Group II : Wheezy child, on drugs at present, no wheeze
- Continue bronchodilators
- Steroids
- Ketamine or Halothane induction
- If possible not to intubate

Group III : Wheezy child, on drugs has active wheeze
- Continue bronchodilators
- Steroids
- Nebulizer
- Risk/Benefit ratio to be explained to the parents.

Anemia

Anemia has been reported to be around 2 percent of pediatric surgical patients. However, it is unlikely that mild anemia would have any discernible impact on the course of anesthesia. Hemoglobin estimation is important to know the base level and if it is low, we should be able to find out the cause of anemia. If it is low we should maintain cardiac output and oxygen saturation. The level of Hematocrit to be taken up for surgery depends upon patients ability to tolerate anemia in the face of expected stresses and blood losses.

Seizures (Fits)

A child with known history of seizure is prone for breakthrough seizures because of:
- Surgical trauma
- Anxiety
- Fasting
- Sleep deprivation

Anticonvulsants should be continued on the day of surgery.

Parenteral anticonvulsants may be needed intraoperatively or in the postoperative period.

Cardiac Murmurs

Often the children referred for preanesthetic assessment have found to have some murmurs. These murmurs may be functional or abnormal murmurs. In general child with a murmur with normal Heart sounds, playing well, acyanotic and is growing well will tolerate a general anesthetic without complication. If there is any suspicion of cardiac abnormality preoperative echocardiogram and evaluation by the pediatric cardiologist are recommended. Antibiotic prophylaxis to prevent bacterial endocarditis is indicated for children with congenital heart disease.

Former Preterm Infant

If the child is preterm, these children are prone for postoperative apnea. The risk of apnea is inversely proportional to the postconceptual age. Employing regional analgesia techniques like caudal epidural or spinal analgesia has reduced the risk of postoperative apnea to a considerable extent. The risk of apnea is there even upto 1 year of age. These neonates may need oral theophylline or intravenous aminophylline in preoperative period to prevent apnoea.

Do the Children Feel Pain?

The children (even neonates) feel pain and there are many studies and research papers to document biochemical and psychological effects of pain on children.

Old Nurses Tales (MYTHS)

Children do not feel pain, they have immature nervous system. Giving analgesic agent depresses respirations and causes addiction.

All of the above are not true.

Why do you Treat Pain?

The physician's main role is:
- to cure sometimes
- to relieve often
- to comfort always "this is true especially for the anesthesiologists."

Adverse Effects of Pain on Various Systems

- Cardiovascular System
  - Increases heart rate and blood pressure
- Respiratory System
  - Decreases tidal volume
  - Decreases FRC
  - Decreases Cough effort

  - Atelectasis
  - Postoperative hypoxia
- Neuroendocrine Response
  - Release of Catecholamines
  - Increases oxygen consumption.
  - Increases carbon dioxide production
  - Hyperglycemia.

All the above effects will adversely affect the child's outcome after surgery.

How to Treat Postoperative Pain?

- Simple analgesics, e.g. Paracetamol (Rectal or oral)
- Nonsteroidal anti-inflammatory drugs, e.g. Ketorolac, Diclofenac
- Narcotics, e.g. morphine, pethidine, fentanyl
- Regional analgesic techniques, e.g. Lignocaine, Bupivicaine, Ropivacaine.

What are the Special Methods Administering Narcotics?

Usually the narcotics like Morphine, Pethidine or Fentanyl are administered as intravenous boluses or intramuscular boluses. But if the hospital has facility and the nurses are used to the infusion pumps the drugs are ideally administered intravenously as continuous infusion.

Side effects are less, as the plasma level of analgesic will be relatively constant using small intravenous increments, and therefore sudden increases with associated side effects, such as respiratory depressions are avoided.

What are the Common Regional Analgesics Techniques Empolyed in Children?

- Penile block for circumcision, hypospadias repair
- Ilioinguinal and iliohypogastric block for herniotomy/orchiopexy
- Single dose caudal epidural for circumcision, herniotomy, lower limb surgeries and lower abdominal surgeries.
- Single dose or continuous lumbar epidural f
- Upper abdominal and lower abdominal sur or hypospadias repair.
- EMLA cream (surface analgesia) for intraver line placement.

Regional analgesia in children is almost alw combined with light general anesthesia to pro excellent postoperative pain relief and e ambulation, with minimal or no need for narco By placing the block before surgery starts but the child is asleep, one can reduce the requiren of general anesthetic agents during surgery, wl in turn may result in a more rapid recovery, ea discharge, less nausea and vomiting and feeds be started early. The types of the regional blc that can be used safely in pediatric anesthetic prac are limited only by the skill and interest of anesthesiologist.

Ten Commandments of Pediatric Anesthesi

1. Good preanesthetic assessment
2. Check availability of proper size instrume
3. Good intravenous line
4. Use of pulse oximeter
5. If in doubt intubate
6. Assist the ventilation
7. If in doubt do not extubate
8. Use regional blocks wherever possible
9. Accompany the child to Recovery Room
10. Visit atleast once in the postoperative war

"The Anesthetic state is not a sleep state rather a state achieved by artificially overpowe the body's most tenacious defenses with som the most dangerous drugs known" ROSS AF-1

So in a nutshell the branch of anesthesia especi pediatric anesthesia is a challenge and it is responsibility of the pediatric anesthesiologis assess the child properly, choose the right anesth technique, monitor the vitals vigilantly and m the Pediatric Surgeon comfortable and the chil be handed over to the mother safely.

Section Eight

Toxic Ingestion

CHAPTER

79

Poisoning and Bites

Anil Sachdev, Mritunjay Pao, RK Mani, Praveen Khilnani

Acute poisoning in children is an important worldwide pediatric emergency. The exact incidence of childhood poisoning is not known in India. The exact magnitude of the problem in our country is not really known due to under reporting and poor record keeping. The National Poison Information Center at the All India Institute of Medical Sciences at New Delhi, was established in 1995 and answers enquiries by telephone and fax. During a three year period between April 1999 to March 2002 the center received a total of 2,720 telephonic queries about poisonings out of which 995(36.6%) were about pediatric poisoning. Males outnumbered females (M=628, F=367). Accidental exposure was common (79.7%), intentional attempts (20.2%) were more common in those older than 12 years. In majority of the cases, the route was oral (96.8%), followed by dermal exposures (3.2%) comprising bites and stings. Commonest agents of exposures were to household products (47.0%), drugs (21.8%), industrial chemicals (7.9%), agricultural pesticides (9.1%), bites and stings (3.2%), miscellaneous products (5.3%) and unknown products. The incidence of poisoning was highest due to household products comprising mainly of pyrethroids, parad/thermometer mercury, rodenticides, phenyl, detergents and corrosives etc. Common drugs ingested included anticonvulsants, thyroid hormones, benzodiazepines, analgesics and oral contraceptives. Among the agricultural pesticides aluminuim phosphide was the commonest followed by organochlorines and organophosphates etc. Paint thinners were the commonest amongst industrial chemicals. Bites and stings were mainly snake bites and scorpion stings. Poisoning due to plants was low most common being Datura.

In a retrospective analysis of all admissions of pediatric poisonings over a 2½ year period in a medical college hospital in South India, the admission rate was 6.9 percent of all annual admissions. Surprisingly, only 19.2 percent were chemical poisonings while biological causes (bites/stings) constituted 80.8 percent of all admissions. This could be due to the fact that the population under study was predominantly rural. The most common chemical agent was kerosene oil (74.87%) followed by drugs and rat killer (7.4% each). Majority of the children were less than 5 years of age with a male preponderance.

One study from a referral hospital from North India reported < 1 percent incidence of poisoning of pediatric admissions in the hospital, while 3 to 4 percent of PICU admissions are because of toxic exposure in western countries. Other Indian figures state that 1 percent of all pediatric admissions are due to poisoning; 75 percent are non-toxic ingestions; 20 percent require urgent measures to remove the poison and only 5 percent of children with poisonings need intensive treatment.

Western literature mentions the oral route to be the most common portal of entry (75%) with dermal, ophthalmic and inhalational routes making up the rest. Most episodes involved only a single agent and approximately 75 percent could be managed at home.

Pediatric poisoning is usually seen in two groups of patients. The first group includes children below 5 years who accidently ingest the toxic substance.

Other potential factors in this group include—male child, hyperactivity, exaggerated hand-mouth activity. Children between 1-3 years are most vulnerable. The other group of children who are prone to poisoning includes adolescent age group. The methodology includes intentional suicidal attempts. The possible risk factors include stress at school or home, conflict with parents, peer pressure and failure in love. Female predominance is seen in this group.

The purpose of this chapter is to provide general management guidelines of a child with suspected or known toxic ingestion, or poisonous bites. Management is essentially supportive, includes the following: (a) Monitoring and support of vital functions, (b) if possible, identification of toxic substance, detoxification and, (c) support and treatment of affected organ system and prevention of further damage.

History, Physical Examination and Monitoring

Detailed history from parents or caretakers of the child usually provides identification of toxic substance. It is important to take history of medications that the child was on or other family members were taking. Route of poisoning and estimated time elapsed from exposure to treatment have an important bearing on therapy indicated and the outcome. Exposure of a young child is usually acute and to single substance. Any important underlying medical illness should be noted. It is important to highlight the effects that occur after the exposure like altered sensorium, seizures, skin color or respiratory pattern changes.

Physical examination of the child should include detailed general and systemic examination besides weight and vital signs. Accurate weight is important to calculate the ingested dose per kilogram and for therapeutic dosing. Skin and clothing retain smell of chemicals like kerosene, pesticides and cleaning agents. Similarly, breath odor may provide diagnostic clues, such as smell of garlic indicating organophosphates, fruity odor breath is present in nail polish remover and bitter almond smell points towards cyanide poisoning. Aberrations in temperature, respiratory pattern, heart rate and blood pressure may help in diagnosis (Tables 79.1 and 79.2).

Admission to the PICU (pediatric intensive care unit) and close cardio-respiratory and pulse oximetry are required besides serial clinical examinations. Repeated physical examination and vital sign charting should be performed by pediatric critical care nurse or resident doctor. It should also include monitoring of neurological status, pupillary size, reactivity and Glasgow coma scale score. Continuous ECG monitoring is indicated in children exposed to cardiotoxic drugs. Arterial line and central venous access may be required in hemodynamically unstable patients for monitoring of arterial blood pressure, blood gas analysis and central venous pressure monitoring, fluid resuscitation as well as inotropic support. Equipment for endotracheal intubation and initiation of mechanical ventilation should be on stand by in-patients with respiratory depression, apnea or respiratory irregularity.

Radiography and Laboratory Assessment (Table 79.3)

Skiagram of skull and spine including CT scan are needed when trauma is suspected in a child with toxic ingestion. Chest radiograph is required in children with respiratory distress, cyanosis and in those patients who may have aspirated stomach contents, at risk for developing acute respiratory distress syndrome. Certain common toxic substances are radio opaque. This may be remembered with mnemonic "CHIPES" chloral hydrate, heavy metals, iodine, phenothiazines, enteric coated, extended release tablets and salt tablets. Gastric aspirate and urine are best samples for toxicologic screening while estimate of toxic substance in serum is less useful, due to limited availability.

Initial Stabilization (Flow chart 79.1)

Initial stabilization of toxic child includes management of airway, breathing and circulation. Certain important points need emphasis. Endotracheal intubation may be required early in toxic child to protect airways. Rapid sequence elective intubation is preferred to emergency intubation after cardio-respiratory arrest. Continuous cardio-respiratory including pulse oximetry are needed for close monitoring of the physiological status. Early detection of hypotension and use of inotropes, as

Table 79.1: Clinical Manifestations of ingestion of various toxic substances

Pulse:	
Bradycardia	Digoxin, Narcotics, Organophosphates, Cyanide, Carbon Monoxide, Clonidine, Beta-blockers, Calcium channel blockers
Tachycardia	Alcohol, Amphetamines, Sympathomimetics, Atropinics, (Atropine and other anticholinergic agents)Tricyclic antidepressants, Theophylline, Salicylates, Phencyclidine, Cocaine
Respiration:	
Slow, depressed	Alcohol, Barbiturates (late), Narcotics, Sedative- Hypnotics
Tachypnea	Amphetamines, Barbiturates (early), Methanol, Salicylates, Carbon monoxide.
Blood Pressure:	
Hypotension	Methemoglobinemia (Nitrates, Nitrites, Phenacetin), Cyanide, Carbon monoxide, Phenothiazines, Tricyclic antidepressants, Barbiturates, Iron, Theophylline, Clonidine, Narcotics, Beta-blockers, Calcium channel blockers.
Hypertension	Amphetamines, Sympathomimetics (especially Phenylpropanolamine in over-the- counter (OTC) cold remedies), Tricyclic antidepressants, Phencyclidine, MAO inhibitors, Antihistamines, Atropinics, Clonidine, Cocaine
Temperature:	
Hypothermia	Ethanol, Barbiturates, Sedative-Hypnotics, Narcotics, Phenothiazines, Antidepressants, Clonidine, Carbamazepine.
Hyperpyrexia	Atropine, Quinine, Salicylates, Amphetamines, Phenothiazines, Tricyclic antidepressants, MAO inhibitors, Theophylline, Cocaine
Neuromuscular:	
Coma	Narcotics, Sedative -Hypnotics, Anticholinergics (Antihistamines, Antidepressants, Phenothiazines, Atropinics), Alcohol, Anticonvulsants, Carbon monoxide, Salicylates, Organophosphate insecticides, Clonidine.
Delirium/Psychosis	Alcohol, Phenothiazines, Drugs of abuse (Phencyclidine, LSD, Mescalline, Marijuana, Cocaine, Heroin, Methaqaulone), Sympathomimetics and Anticholinergics (including prescription and OTC cold remedies), Steroids, Heavy Metals
Convulsions	Alcohol, Amphetamines, Cocaine, Phenothiazines, Antidepressants, Antihistamines, Camphor, Boric acid, Organophosphates, Isoniazid, Salicylates, Lindane, Lidocaine, Phencyclidine
Ataxia	Alcohol, Barbiturates, Carbon monoxide, Diphenylhydantoin, Heavy metals, Organic solvents, Sedative/Hypnotics, Hydrocarbons
Paralysis	Botulism, Heavy metals, Tick paralysis, Shellfish Poisoning.
Eyes:	
Miosis	Narcotics, Organophosphates, Plants (Mushrooms of muscarinic type), Ethanol, Barbiturates, Phenothiazines, Phencyclidine, Clonidine
Mydriasis	Amphetamines, Atropinics, Barbiturates (if comatose), Cocaine, Methanol, Glutethimide, LSD, Marijuana, Phencyclidine, Antihistamines, Antidepressants
Nystagmus	Diphenylhydantoin, Sedative-Hypnotics, Carbamazepine, Glutethimide, Phencyclidine, Barbiturates, Ethanol
Skin:	
Jaundice	Carbon tetrachloride, Acetaminophen, Naphthalene, Phenothiazines, Plants (Mushrooms, Fava Beans), Heavy Metals (Iron, Phosphorus, Arsenic)
Cyanosis	Methemoglobinemia due to Aniline dyes, Nitrites, Benzocaine, Phenacetin, Nitrobenzene, Phenazopyridine
Flushing to reddish discoloration	Atropine, Antihistamines, Alcohol, Carbon Monoxide, Cyanide, Boric acid
Smell:	
Acetone	Acetone, Isopropyl alcohol, Phenol and Salicylates
Alcohol	Ethanol (Alcoholic beverages)
Bitter Almond	Cyanide
Garlic	Heavy Metal (Arsenic, Phosphorus and Thallium), Organophosphates
Hydrocarbons	Hydrocarbons (Gasoline, Turpentine, etc.)

Table 79.2: Common pediatric toxidromes

Toxin	*Signs and Symptoms*
Opiates	Miosis, coma, hypotension, and bradycardia.
Anticholinergics	Fever, flushed dry skin, mydriasis, dry mouth, delirium, and tachycardia.
Cholinergics	SLUDGE syndrome (salivation, lacrimation, urination, defecation, garlic odour, emesis) with miosis.
Tricyclic antidepressants	Seizures, coma, acidosis, dysrhythmias, hypotension, prolonged QRS interval.

Table 79.3: Laboratory investigations indicated in a child with toxic ingestion

- Complete Blood Count
- Coagulation Profile
- Methemoglobin level (if indicated)
- Renal function test
- Liver function test
- Blood gas analysis
- Serum Osmolarity and Osmolar gap estimation
- Serum analysis for ingested substance/ drug level
- Urine toxic screen

well as control of seizures with antiepileptic drugs needs no emphasis. Repeated examination of toxic child for early detection of rapidly changing clinical signs is mandatory and cannot be replaced.

Decontamination

Before attempting decontamination, the medical personnel must protect themselves from possible toxic exposure.

Gastrointestinal Decontamination (GID)

The removal of toxic products from gastrointestinal tract includes: 1) emesis, 2) gastric lavage, 3) activated charcoal, 4) cathartics and 5) whole bowel irrigation.

Emesis

Induced emesis with syrup of Ipecac is most effective when used soon after ingestion (within one hour). It has been claimed to remove about 30 to 40 percent of ingested toxin and is efficacious in about 90 percent of patients. It is useful in home management for early emesis. The recommended dose of syrup of Ipecac varies with age:

Between 6 months-1 year	– 10 ml
1-12 years	– 15 ml
Adolescents	– 30 ml

This should be followed by 50-150 ml of water.

Ipecac should be avoided in children below 6 months of age, in the presence of altered sensorium, hydrocarbon or caustic ingestion, coagulopathy, gastrointestinal bleeding, co-ingestion of sharp foreign body and significant vomiting before Ipecac ingestion.

The reported side effects of syrup of Ipecac are persistent vomiting, diarrhea, CNS (central nervous system) depression, esophageal tears, delay in use of activated charcoal, rarely pneumomediastinum and intracranial bleeding.

Gastric Lavage

Gastric lavage is an alternative to syrup of Ipecac and is more useful when performed in the first hour of ingestion. Initial lavage may be used for analysis. The procedure can be performed in patients with altered sensorium after securing airway. Recommended orogastric tube size in less than 3 years is 28 F (French), 28-36 F in children aged 3-12 years and 36-40 F in adolescents. Warm 0.9 percent saline or tap water are used for lavage. Volume of fluid varies with the age of the child. Usually it is 15 ml/kg and in adolescents upto 200 ml is used. Lavage is continued till clear fluid is obtained or 1-2 litres has been exchanged.

Gastric lavage should be avoided after ingestion of strong acid or alkali, ingestion of sharp materials or non-toxic substance and in the presence of bleeding diathesis. Complications are uncommon but include esophageal or gastric perforation, pulmonary aspiration, and electrolyte imbalance.

Activated Charcoal

Activated Charcoal is an inert, non-toxic and non-absorbable material with large surface area to adsorb almost any toxic, inorganic or organic substance most

Table 79.4: Antidote therapy for poisonings

Toxin	*Antidote*	*Pediatric Dose*
Acetaminophen	N-acetylcysteine	Loading dose: 140 mg orally; Maintenance doses: 70 mg/kg every 4 hrs for 17 doses orally.
Anticholinergics	Physostigmine salicylate	0.02 mg/kg slow IV infusion over 3-5 minutes titrated to effect
Arsenic	Succimer (DMSA #)	10 mg/kg orally 3 times a day
	British anti-Lewisite (BAL) (dimercaprol) only if unable to tolerate oral succimer	3-5 mg/kg intramuscular every 4-6 hours
Benzodiazepines	Flumazenil	0.01 mg/kg IV bolus titrated to effect or total dose of 1-3 mg
β-blockers	Glucagon	0.15 mg/kg IV bolus, then 0.1 mg/kg/h IV infusion titrated to effect.
Calcium channel blockers	Calcium chloride	10 percent 0.1-0.2 ml/kg IV bolus, repeat doses and IV infusions are commonly required.
	Glucagon	0.15 mg/kg IV bolus followed by 0.1 mg/kg/h IV infusion titrated to effect.
Carbamates	Atropine	0.1 mg/kg IV bolus, repeat doses titrated to effect.
Cyanide	Cyanide antidote kit: Sodium nitrite 3 percent	0.15-0.33 ml/kg to maximum of 300 mg slow IV infusion.
	Sodium thiosulfate	400 mg/kg up to 12.5 g IV infusion.
Digoxin	Digoxin immune antibody fragment (Digibind)	Empiric dosing: 10-20 vials IV bolus for life threatening toxicity (see package insert for other dosing regimens)
Ethylene glycol, Methanol	Ethanol 10 percent	Loading dose 10 ml/kg IV or orally followed by maintenance dose 1-2 ml/kg/h IV infusion or orally.
	Fomepizole	15 mg/kg IV bolus, repeat doses may be necessary.
Iron	Desferoxamine	5-15 mg/kg/h IV infusion
Isoniazid	Pyridoxine	1 g per gram ingested or emperic dosing 75 mg/kg IV bolus up to 5 g.
Lead	Succimer (DMSA) if patient is able to tolerate oral medication	10 mg/kg orally 3 times a day, repeat doses are common.
	BAL (dimercaprol) (only for lead encephalopathy)	3-5 mg/kg IM or 50-75 mg/m^2
	Calcium disodium EDTA	20-30 mg/kg diluted in 250 ml IV infusion over 12-24 hours (start 4 hours after BAL administration).
Methemoglobinemia	Methylene blue	1-2 mg/kg slow IV infusion, repeat doses as needed
Opioids	Naloxone hydrochloride	0.4-2 mg IV titrated to effect (0.01-0.1 mg/kg)
Organophosphates	Atropine	0.1 mg/kg IV bolus, repeat dose titrated to effect.
	Pralidoxime	25-50 mg/kg slow IV infusion (maximum 200 mg/min) followed by 5-10 mg/kg/h continuous infusion or 20 mg/kg every 4 hours.
Salicylates	Sodium bicarbonate	150 mEq + 40 mEq KCl in one litre of D5 w infused to maintain urine output at 1-2 mL/kg/h and a urine pH approximately 7.5
Tricyclic Antidepressants	Sodium bicarbonate	1-2 mEq/kg IV bolus, titrate repeat boluses (do not exceed arterial pH 7.55)
Warfarin, Superwarfarins	Fresh frozen plasma	Fresh frozen plasma for life threatening hemorrhage.
	Vitamin K1	0.6 mg/kg slow IV infusion, subcutaneously or orally.

efficaciously. The vast network of fine pores acts as chemical traps to absorb and transport out toxic substance. Recommended dose of activated charcoal is 1 gm/kg diluted 1:4 in well mixed slurry. Tablets of activated charcoal are not useful. This slurry is taken orally if child is cooperative and alert or through orogastric or nasogastric tube. Cathartic may be administered with initial dose of charcoal to counter the constipating effect of charcoal. Multiple doses of activated charcoal are used to treat toxicity due to digoxin, phenobarbitone, theophylline, dapsone, methotrexate, amitriptyline, aspirin and many others. Activated charcoal is not effective for caustics, hydrocarbons, iron, methanol, ethanol, ethylene glycol and certain heavy metals. This procedure is contraindicated in the presence of ileus or mechanical obstruction. Activated charcoal use should be avoided if endoscopy is anticipated. Rarely, complications are seen with use of activated charcoal which include aspiration into lungs, intestinal obstruction and constipation.

Catharsis

Catharsis is usually used as an adjunct to activated dry charcoal to enhance gastrointestinal mobility and reduce the absorption of non-absorbable toxic substances. Commonly used cathartic in pediatric patients include 70 percent Sorbitol (1-2 ml/kg), 10 percent Magnesium Citrate (3-4 ml/kg), and Magnesium Sulphate (250 mg/kg). Contraindications include paralytic ileus, gastro-enteritis, abdominal trauma, intestinal obstruction and renal failure. Complications include severe fluid loss, electrolyte imbalance, hyperosmolarity and abdominal cramps.

Whole Bowel Irrigation

This procedure is performed with solutions like poly-ethyleneglycol with minimal fluid and electrolyte problems. It is useful in situations when activated charcoal is less or not effective such as iron, heavy metal poisoning and after ingestion of enteric coated or sustained release tablets. Contra-indications include paralytic ileus and mechanical obstruction. Complications include excessive fluid loss per rectum and vomiting. This procedure reduces the effectiveness of activated charcoal. Dose of fluid is 25 ml/kg/hour through nasogastric tube or orally till rectal effluent is clear.

Toxin Elimination Enhancement

These are occasionally used invasive methods to enhance toxin elimination under specific circumstances. These methods include urinary pH manipulation, peritoneal or hemodialysis, hemofiltration, charcoal hemoperfusion and exchange transfusion. Alkalinization of urine (pH > 7.0) is useful in salicylate overdose. Peritoneal dialysis is less effective than hemodialysis and is useful for low molecular weight toxins like salicylate, lithium and alcohol.

Specific Antidote Therapy (Table 79.4)

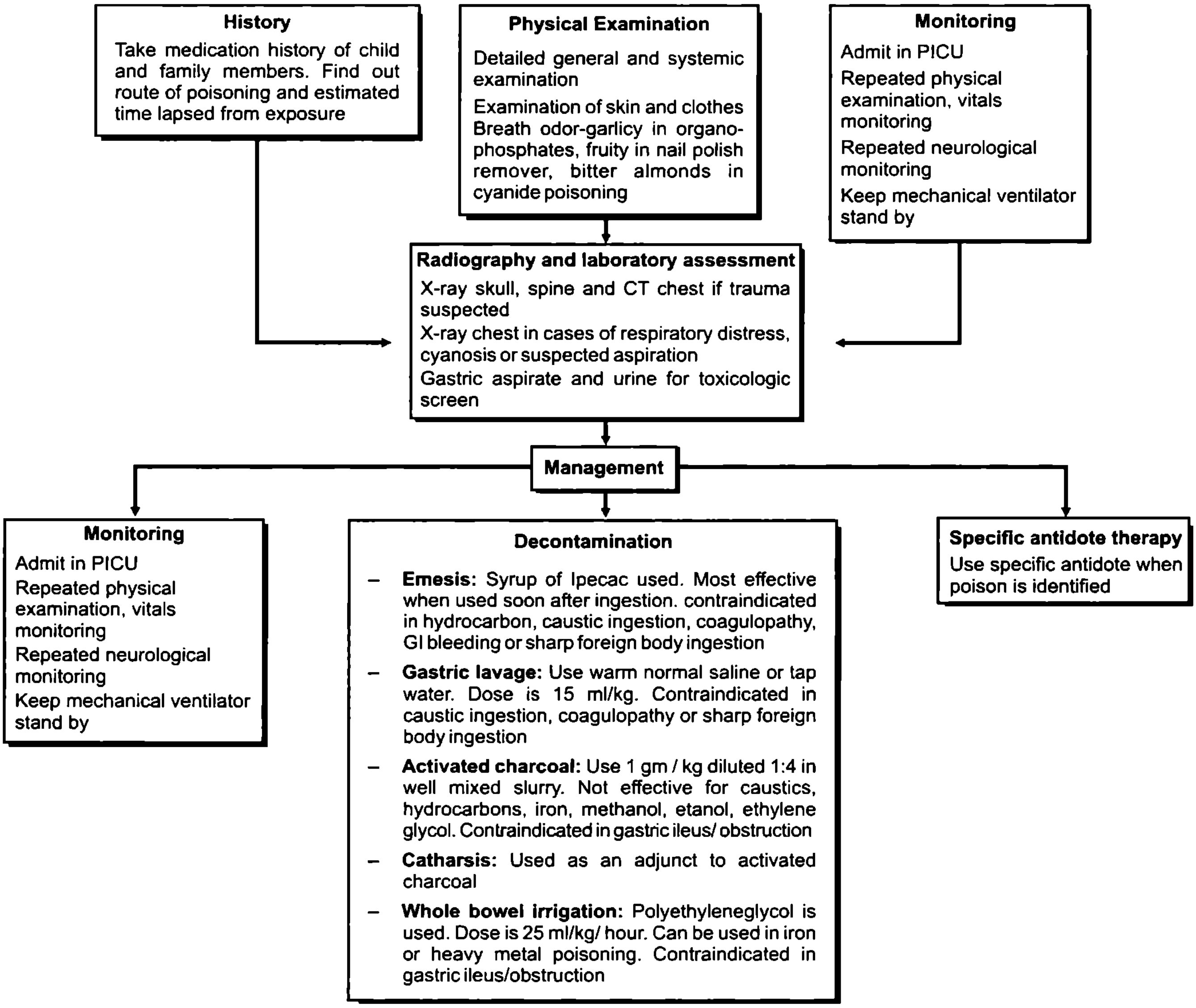
Specific antidotes are available for limited offending agents, so meticulous general and supported care is needed by majority of children.

Antidotes

Commonly used antidotes and their doses are as follows:

1. ***Atropine***: Used in organophosphorus and carbamate poisoning in a dose of 0.02 mg/kg intravenously (IV) repeated every 5 to 10 min. till patient is atropinized (heart rate increases, pupils dilate).
2. ***Deferoxamine***: Used in iron poisoning, if the patient is normotensive and poisoning is mild, 50 mg/kg IM (intramuscularly) every 4 hours. In case of severe poisoning or hypotension, 15 mg/kg/hr IV for 4 hours then 2 to 5 mg/kg/hr (Maximum daily dose is120 mg/kg or 6 gm; whichever is less).
3. ***Flumazenil***: Used in benzodiazepines overdose. It is used IV at doses ranging from (0.01 mg/kg) 0.2 to 0.5 mg over 30 sec. (Maximum dose 1–3 mg).
4. ***Naloxone***: Used in a doses of 0.01 mg/kg to 0.1 mg/kg in cases of narcotics poisoning. IV or via endotracheal route.
5. ***Physostigmine***: Given as an antidote for poisoning with anticholinergics. The dose used is 0.02 mg/kg IV as a slow push.
6. ***Pralidoxime***: Used in organophosphorus poisoning in a dose of 25 to 50 mg/kg over 5 to 10 minutes not exceeding 200 mg/minute; maximum 2 g) followed by 5-10 mg/kg/hour infusion or 20 mg/kg every 4 hours. It is useful only if given within 30 hours of exposure (see Flow chart 79.1).

Flow chart 79.1: Approach to a child with poisoning



History

Take medication history of child and family members. Find out route of poisoning and estimated time lapsed from exposure

Physical Examination

Detailed general and systemic examination

Examination of skin and clothes Breath odor-garlicy in organophosphates, fruity in nail polish remover, bitter almonds in cyanide poisoning

Monitoring

Admit in PICU

Repeated physical examination, vitals monitoring

Repeated neurological monitoring

Keep mechanical ventilator stand by

Radiography and laboratory assessment

X-ray skull, spine and CT chest if trauma suspected

X-ray chest in cases of respiratory distress, cyanosis or suspected aspiration

Gastric aspirate and urine for toxicologic screen

Management

Monitoring

Admit in PICU

Repeated physical examination, vitals monitoring

Repeated neurological monitoring

Keep mechanical ventilator stand by

Decontamination

- **Emesis:** Syrup of Ipecac used. Most effective when used soon after ingestion. contraindicated in hydrocarbon, caustic ingestion, coagulopathy, GI bleeding or sharp foreign body ingestion
- **Gastric lavage:** Use warm normal saline or tap water. Dose is 15 ml/kg. Contraindicated in caustic ingestion, coagulopathy or sharp foreign body ingestion
- **Activated charcoal:** Use 1 gm / kg diluted 1:4 in well mixed slurry. Not effective for caustics, hydrocarbons, iron, methanol, etanol, ethylene glycol. Contraindicated in gastric ileus/ obstruction
- **Catharsis:** Used as an adjunct to activated charcoal
- **Whole bowel irrigation:** Polyethyleneglycol is used. Dose is 25 ml/kg/ hour. Can be used in iron or heavy metal poisoning. Contraindicated in gastric ileus/obstruction

Specific antidote therapy

Use specific antidote when poison is identified

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TOXICITY OF SPECIFIC AGENTS

HYDROCARBONS EXPOSURE

Exposure to hydrocarbons is common in children because they are easily accessible in households especially products such as kerosene, petrol, turpentine, furniture polish, household cleansers, propellants, and other fuels. Kerosene poisoning is the commonest accidental poisoning in India, due to widespread use as a domestic fuel for cooking and being stored in water and cold drink bottles. Jayashree et al reported that hydrocarbon ingestion constituted 35 percent of all poisonings admitted to their PICU, kerosene being the commonest. Most of the toxic hydrocarbons are derived from petroleum distillates and include aliphatic (straight-chain) hydrocarbons and aromatic (benzene-containing) hydrocarbons. Other hydrocarbons such as pine oil and turpentine are derived from wood.

CLINICAL FEATURES

Pulmonary

Pulmonary toxicity occurs due to aspiration the volatile hydrocarbon which displaces alveolar oxygen, leading to hypoxia. Direct contact with alveolar membranes can lead to hemorrhage, hyperemia, edema, surfactant inactivation, leukocyte infiltration, and vascular thrombosis (chemical pneumonitis). The result is poor oxygen exchange, atelectasis and necrotising pneumonitis.

Respiratory symptoms like gasping, choking, grunting, coughing, and intercostal retractions are the earliest signs of hydrocarbon ingestion. Most patients are symptomatic by 4 hours. Delayed presentation at 48 hours indicates superimposed bacterial infection. All symptomatic patients should get a chest X-ray radiographic abnormalities, the commonest being bilateral lower lobe infiltrates. Complications include hypoxia, barotrauma due to mechanical ventilation, and adult respiratory distress syndrome (ARDS). Prolonged hypoxia may result in encephalopathy, seizures and death.

Gastrointestinal

GI manifestation is due to local irritation by the ingested hydrocarbon. Abdominal pain and nausea are common complaints. Vomiting increases the likelihood of pulmonary aspiration.

CNS

Symptoms of central nervous system (CNS) agitation or depression including drowsiness, restlessness, alternating drowsiness and restlessness, stupor and convulsions. Eventually, lethargy, headache, obtundation and coma may follow. Seizures are uncommon and are due to hypoxia.

Cardiac

Hypoxia, myocardial sensitization to catecholamines, and direct myocardial damage may cause dysrhythmias. Sudden death has been reported as a result of coronary vasospasm due to hydrocarbon inhalation.

Fever

In cases of hydrocarbon aspiration, the patient's temperature may be elevated due to the body's reaction to the foreign substance.

Investigation: Blood gas (ABG) analysis is useful in documenting hypoxemia in severely affected patients revealing hypercarbia in patients with respiratory depression and decreased gas exchange. A chest radiograph must be obtained in all symptomatic patients. Initially, the chest radiographic results may be normal, but positive findings may develop over the first few hours after ingestion. Common findings include fine perihilar opacities, bibasilar infiltrates, and atelectasis. If discharge is being considered for an asymptomatic patient, a chest radiograph should be obtained 6 hours after the ingestion to document the negative findings.

Emergency Management (Flow chart 79.2)

All patients presenting with hydrocarbon poisoning to emergency are admitted and treated with a standard protocol consisting of skin decontamination, maintenance of oxygenation, fluid and electrolyte balance and ventilation, if required. Hypoxemia was defined as $PaO_2 < 60$ mm Hg in room air, on arrival. Stabilize the airway, give supplemental oxygen to all patients, and perform beside pulse oximetry. Early intubation, mechanical ventilation, and use of positive end-expiratory pressure should be considered patients in whom oxygenation is inadequate or in a patient who has severe respiratory distress or a decreased level of consciousness. Gastric lavage is avoided to minimize the patient's risk of vomiting and further aspiration. Any change in the patient's clinical respiratory symptoms warrants repeat chest radiography, which may demonstrate new and important changes. Clean the skin as soon as possible by removing the involved clothing and thoroughly washing the skin with soap and water. Vapor inhalation and cutaneous absorption may occur long after the exposure.

Gastric decontamination: Regardless of the amount involved, gastric emptying is not indicated for accidental ingestion of a hydrocarbon lacking systemic toxicity. This represents the majority of cases. The risk of aspiration during vomiting or lavage far outweighs any benefit from removal of the substance.

Lavage is useful in cases in which the hydrocarbon has an inherent systemic toxicity or contains additives with known toxicity. A useful mnemonic for remembering such hydrocarbons is CHAMP, which stands for camphor, halogenated hydrocarbons, aromatic hydrocarbons, (heavy) metal-containing hydrocarbons, and pesticide-containing hydrocarbons. Activated charcoal is indicated only in cases of a suicide attempt or in cases in which another adsorbable toxic substance have been co-ingested. Prior lavage, hypoxemia at admission, need for ventilation, secondary sepsis and ventilator related complications were associated with poor outcome, these patients are given priority for admission to the PICU.

Steroids have not been shown to be useful. Antibiotics should be reserved for documented infection. A beta-2 selective agonist can be given for bronchospasm, while epinephrine should be avoided as it may precipitate dysrhythmias.

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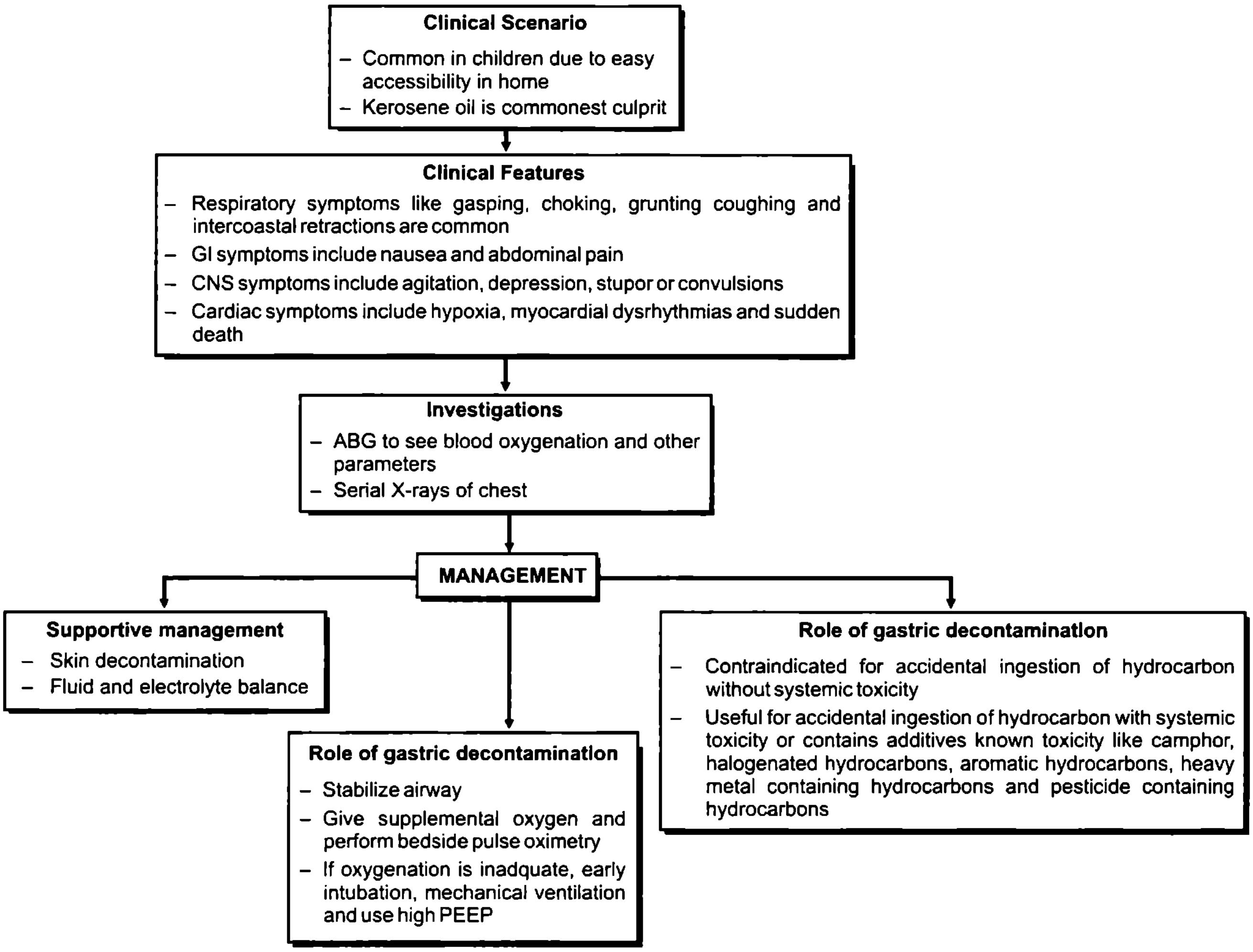
Flow chart 79.2: Hydrocarbon exposure



Clinical Scenario

- Common in children due to easy accessibility in home
- Kerosene oil is commonest culprit

Clinical Features

- Respiratory symptoms like gasping, choking, grunting coughing and intercoastal retractions are common
- GI symptoms include nausea and abdominal pain
- CNS symptoms include agitation, depression, stupor or convulsions
- Cardiac symptoms include hypoxia, myocardial dysrhythmias and sudden death

Investigations

- ABG to see blood oxygenation and other parameters
- Serial X-rays of chest

MANAGEMENT

Supportive management

- Skin decontamination
- Fluid and electrolyte balance

Role of gastric decontamination

- Stabilize airway
- Give supplemental oxygen and perform bedside pulse oximetry
- If oxygenation is inadquate, early intubation, mechanical ventilation and use high PEEP

Role of gastric decontamination

- Contraindicated for accidental ingestion of hydrocarbon without systemic toxicity
- Useful for accidental ingestion of hydrocarbon with systemic toxicity or contains additives known toxicity like camphor, halogenated hydrocarbons, aromatic hydrocarbons, heavy metal containing hydrocarbons and pesticide containing hydrocarbons

ORGANOPHOSPHATES

Organophosphates cause irreversible inhibition of cholinesterase thereby leading to accumulation of acetylcholine and excess parasympathetic activity. Organophosphates are widely used as insecticides, because of their rapid breakdown into environmentally safe products. The majority of organophosphate poisoning occurs by accidental or occupational exposure, but poisoning may also be due to suicide attempts, homicide attempts, or chemical warfare. In a child less than one year of age with an organophosphate poisoning, child abuse or neglect may be suspected. In anyone older than 6 years of age, a suicide attempt should be considered in the differential. Health care workers must be very cautious to prevent self-contamination when caring for an exposed patient. When caring for a patient with organophosphate poisoning, it is important to remember than any vomited material should be treated as a chemical spill.

Clinical Features

The most life-threatening symptoms are respiratory and cardiac in nature. The patient can have wheezing, chest tightness, and a productive cough. The bronchorrhea can be significant with frothy and/or bloody sputum and severe pulmonary edema. The most common cardiac findings are bradycardia and hypotension. Cardiac depression and cardiovascular collapse may occur, and toxic cardiomyopathy may be present in severe poisonings. Dysrhythmias that may be encountered include atrial fibrillation, AV blocks, torsades de pointes, or asystole. Miscellaneous effects to be aware of include pancreatitis, hyperglycemia, hypothermia, and a characteristic garlic odor that may aid in diagnosis when an unknown toxin has been ingested.

The clinical picture correlates poorly with measured cholinesterase activity and includes headache, dizziness, and the "SLUDGE" syndrome (Salivation, Lacrimation, Urination, Defecation, GI distress, Emesis) which is due to the muscarinic effects of acetyl choline. When cholinesterase activity is 10-20 percent of baseline, the patient will likely experience generalized weakness, difficulty speaking, fasciculations, and miosis; this is moderate poisoning. In severe poisoning the cholinesterase level is generally less than 10 percent of baseline; these patients are likely to have the most severe symptoms as described above.

The Nicotinic effect causes early stimulation which is followed by paralysis of the pre ganglionic and somatic nerve fibers leading to twitching of eyelids, tongue and facial muscles, followed by depression of the CNS.

TREATMENT (FLOW CHART 79.3)

Treatment consists of decontamination, supportive care, symptom management, and reactivation of AchE when possible.

Stabilize the airway breathing and circulation: The patient may require intubation to using the rapid sequence intubation technique to protect the airway in severe poisoning. Succinyl choline should be avoided because it a depolarizing agent and also increases secretion. The patient should be well oxygenated before treatment of symptoms, as administration of atropine may precipitate ventricular dysrhythmias in a patient that has poor tissue oxygenation.

Decontamination: All clothing should be removed and bagged as hazardous materials. The patient should be washed thoroughly with soap and water. It is during this skin decontamination that healthcare workers are in the most danger of exposure. In the case of ingestion, GI decontamination can be accomplished via gastric lavage; activated charcoal may be used, although it is not expected to bond well to organophosphates. Many patients will be vomiting profusely and will not require further GI decontamination. Treating personnel should take care to avoid contact with contaminated skin, clothing, or body fluids.

Specific Treatment

Atropine: It neutralizes the muscarinic effect of acetyl-choline. It is used to counteract the symptoms of the poisoning only and does not reverse the effects of the organophosphate on acetylcholinesterase. Atropine should be given IV when available; alternative routes of administration include IM, via ET tube, or nebulized in the case of inhalation poisoning or any time that pulmonary symptoms dominate the clinical picture. The initial dosage is 0.01 mg/kg in children (maximum: 2mg), repeated every 10 minutes until clearing of secretions (note that pupillary changes are not a sufficient marker for the endpoint of treatment). Treatment may require very large doses of atropine, up to several grams per day. Tachycardia and dilated pupils are not contraindications for atropine administration when given for an acute organophosphate poisoning.

Glycopyrroate: Can be used in young infants and neonates since it is less likely to produce tachycardia. It does not cross the blood brain barrier resulting in less CNS toxicity in large doses required for treatment.

Pralidoxime (PAM): Organophosphates deactivate AChE by phosphorylation. After a period of time, this bond matures or ages and becomes irreversible. However, within the first 24-72 hours following acute poisoning, the AChE-OP compound has not aged and the phosphorylation can be reversed by administration of pralidoxime (PAM), thereby reactivating the AChE. PAM should be given as soon as possible after a poisoning is recognized in order to re-activate the highest possible number of AChE molecules. As PAM has very little toxicity at therapeutic levels, it is better to err on the side of PAM administration should an OP poisoning be suspected.

The pediatric dose is 20 to 40 mg/kg IV over 30 minutes. It can also be given as a infusion, initially a loading dose is given followed by a continuous infusion of 10-20 mg/kg/hr. The end point of treatment should be determined by symptom resolution with concomitant lab testing for cholinesterase activity Fat-soluble organophosphates may have a prolonged release and potential to cause recurrent symptoms after therapy has been discontinued. PAM should be given as early as possible, and probably is not useful if given 36 hours after exposure. Adverse effects of 2-PAM are minimal unless plasma levels are high. When present, these effects may include dizziness, blurry vision and diastolic hypertension. Rapid intravenous administration may lead to respiratory or cardiac arrest.

CARBAMATES

The carbamates Carbofuran (Furadan), Propoxur (Baygon), Bufencarb (Bux) are commonly used as insecticides. Their mode of action is similar to the organophosphates although they are less toxic because they do not penetrate the blood brain barrier and they have a short duration of action. Carbamate poisoning is similar to treatment of organophosphates.

FURTHER READING

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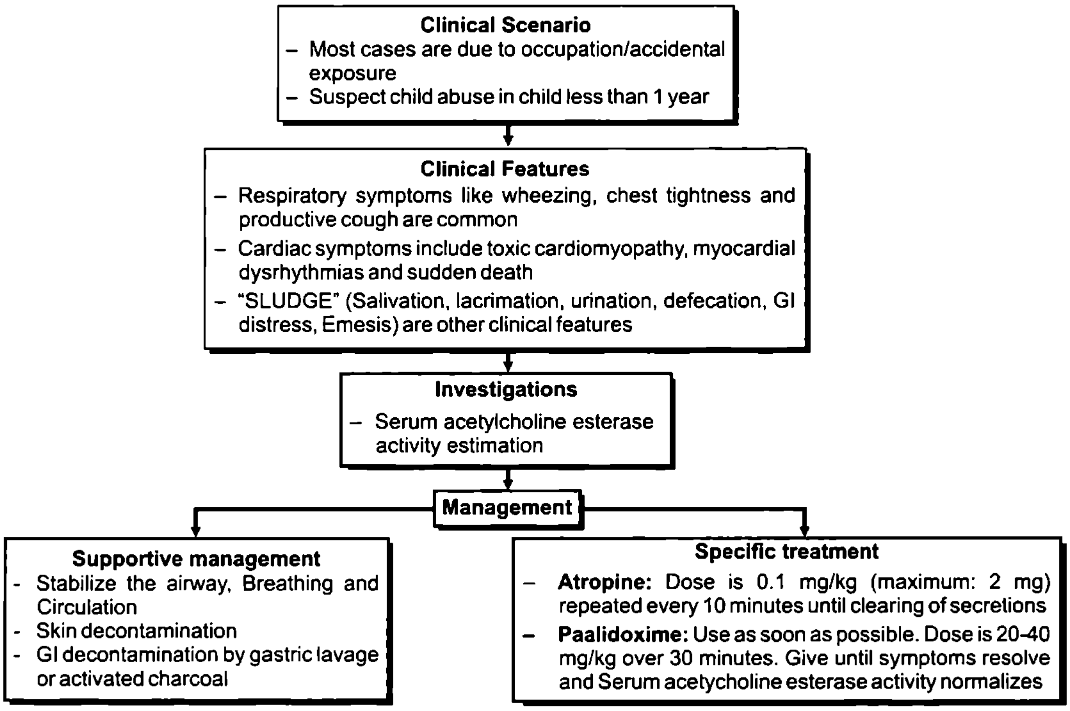
Flow chart 79.3: Organophosphate toxicity



Clinical Scenario
- Most cases are due to occupation/accidental exposure
- Suspect child abuse in child less than 1 year

Clinical Features
- Respiratory symptoms like wheezing, chest tightness and productive cough are common
- Cardiac symptoms include toxic cardiomyopathy, myocardial dysrhythmias and sudden death
- "SLUDGE" (Salivation, lacrimation, urination, defecation, GI distress, Emesis) are other clinical features

Investigations
- Serum acetylcholine esterase activity estimation

Management

Supportive management
- Stabilize the airway, Breathing and Circulation
- Skin decontamination
- GI decontamination by gastric lavage or activated charcoal

Specific treatment
- **Atropine:** Dose is 0.1 mg/kg (maximum: 2 mg) repeated every 10 minutes until clearing of secretions
- **Paalidoxime:** Use as soon as possible. Dose is 20-40 mg/kg over 30 minutes. Give until symptoms resolve and Serum acetycholine esterase activity normalizes

PARACETAMOL

Paracetamol is the most commonly used drug in pediatrics. It has an excellent safety profile in therapeutic doses, but hepatotoxicity can develop with overdoses. Paracetamol poisoning is most often accidental in children below 6 years of age but in adolescents it is often associated with suicidal attempts and is potentially serious. Paracetamol is nontoxic, but hepatic metabolism leads to formation of a toxic metabolite, N-acetyl-benzoquinoneimine (NAPQI). The liver metabolizes more than 90 percent of acetaminophen to glucuronide and sulfate conjugates, which are eliminated in the urine. In children, sulfation is the primary pathway until age 10-12 years; glucuronidation predominates in adolescents and adults. Only a small amount of paracetamol (2%) is excreted unchanged by the kidney. Hepatotoxicity is the result of formation of the reactive and toxic metabolite NAPQI by the cytochrome P-450 system. The maximum daily dose of paracetamol is 90 mg/kg in children (4 g in adults). A single ingestion of more than 150 mg/kg in a child is a potentially toxic dose of paracetamol. Diagnosis is based in the history of ingestion, clinical features and plasma levels of paracetamol.

Clinical Features

In acute exposures, mortality and morbidity are decreased in pediatric patients compared to mortality and morbidity in adults. Stage 1 lasts up to 24 hours, patients experience anorexia, nausea and vomiting. Stage 2 occurs 24-48 hours postingestion. Patients present with right upper quadrant pain and tenderness that coincides with transaminase elevation. Stage 3 develops 3-4 days postingestion when symptoms of hepatic failure with jaundice, bleeding, or encephalopathy 3.5 percent of patients who develop hepatotoxicity eventually develop fulminant hepatic failure. Death may occur due to cerebral edema or sepsis. Stage 4 occurs 4-14 days postingestion. This is the stage of recovery the hepatic enzyme levels come down. In some patients increased transaminase levels may persist longer.

The Rumack-Matthew normogram uses a single level in time to predict the risk of hepatotoxicity. It does not predict fulminant hepatic failure or death. Normogram tracking begins at 4 hours postingestion and ends at 24 hours postingestion. The upper line is the probable line, and 60 percent of patients with plots above this line develop hepatotoxicity. The lower line is the possible line, which was added to the nomogram to give a 25 percent margin of error to allow for variations in measurement of paracetamol level or uncertainty of ingestion.

Laboratory Features

Hepatotoxicity in Paracetamol poisoning is defined by elevation of the plasma transaminase above 1,000 U/L which start to rise within 24 hours of ingestion and peaks at 48-72 hours postingestion. In severe overdose, transaminase elevation can develop as early as 12-16 hours after ingestion. However, it is important to monitor liver function through coagulation studies. Renal function tests may show evidence of renal failure, which often occurs with hepatic failure. Rarely, renal failure may occur without hepatic failure.

TREATMENT (FLOW CHART 79.4)

Gastric lavage should not be routinely done for gastric decontamination, but should be limited to patients with recent (within 60 min) and potentially life-threatening toxicity. Most pediatric patients can be treated with activated charcoal alone.

Gastrointestinal Decontamination

Activated charcoal decontamination is done in any patient who presents within 4 hours of ingestion. Activated charcoal absorbs paracetamol, but its use has been controversial since oral NAC also is absorbed by activated charcoal. Although activated charcoal reduces NAC bioavailability to a statistically significant degree, the small decrease in the NAC bioavailability is unlikely to reduce the effectiveness of NAC as an antidote.

N-Acetyl Cysteine (NAC)

The antidote for paracetamol toxicity is NAC, which has several mechanisms to prevent hepatotoxicity. NAC is converted to cysteine, which can replenish glutathione stores. NAC also directly detoxifies NAPQI to nontoxic metabolites. NAC can provide a substrate for sulfation, thereby increasing the capacity for nontoxic metabolism. NAC can directly conjugate NAPQI to reduce toxicity.

Oral NAC is safe and effective as many as 24 hours after a toxic ingestion. Treatment with oral NAC prevents hepatotoxicity regardless of the initial acetaminophen concentration if NAC is started within 8 hours of ingestion. Effectiveness did not depend on whether NAC was started at 0-4 or 4-8 hours postingestion. Oral NAC is available as a 20 percent concentrate, its strong sulphur like odor is often not acceptable to children. It is prepared by mixing one part in three parts of a carbonated beverage to make it more palatable. The oral loading dose is 140 mg/kg followed by 70 mg/kg every 4 hours for three days upto a total dose of 17 doses.

Intravenous administration of oral NAC is recommended for those with gastrointestinal bleeding or obstruction, potential fetal toxicity from maternal toxicity, or an inability to tolerate oral NAC. It is used in unconscious patients or those who refuse to take it orally.

Liver transplantation possible criteria for liver transplantation include metabolic acidosis, renal failure, coagulopathy, and hepatic encephalopathy.

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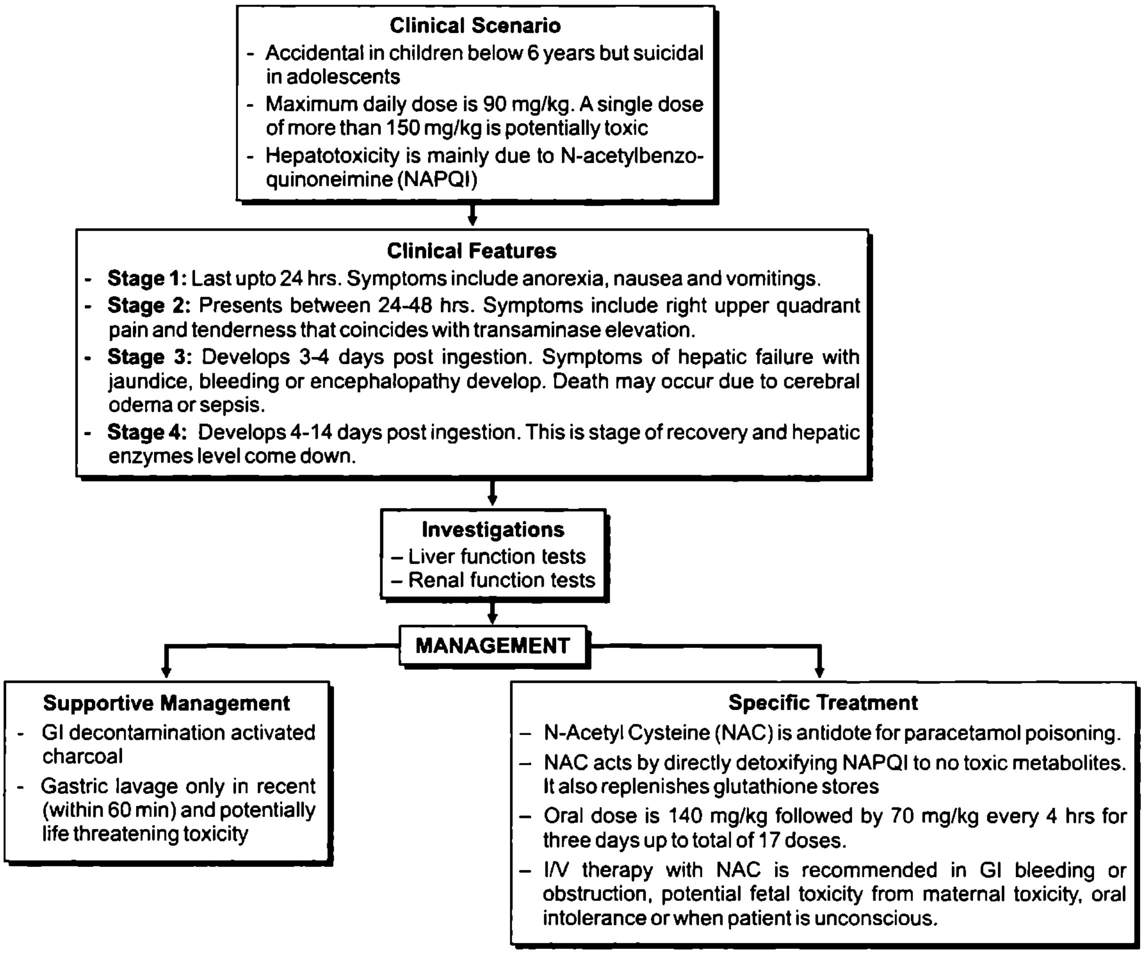
Flow chart 79.4: Paracetamol poisoning



Clinical Scenario
- Accidental in children below 6 years but suicidal in adolescents
- Maximum daily dose is 90 mg/kg. A single dose of more than 150 mg/kg is potentially toxic
- Hepatotoxicity is mainly due to N-acetylbenzoquinoneimine (NAPQI)

Clinical Features
- **Stage 1:** Last upto 24 hrs. Symptoms include anorexia, nausea and vomitings.
- **Stage 2:** Presents between 24-48 hrs. Symptoms include right upper quadrant pain and tenderness that coincides with transaminase elevation.
- **Stage 3:** Develops 3-4 days post ingestion. Symptoms of hepatic failure with jaundice, bleeding or encephalopathy develop. Death may occur due to cerebral odema or sepsis.
- **Stage 4:** Develops 4-14 days post ingestion. This is stage of recovery and hepatic enzymes level come down.

Investigations
- Liver function tests
- Renal function tests

MANAGEMENT

Supportive Management
- GI decontamination activated charcoal
- Gastric lavage only in recent (within 60 min) and potentially life threatening toxicity

Specific Treatment
- N-Acetyl Cysteine (NAC) is antidote for paracetamol poisoning.
- NAC acts by directly detoxifying NAPQI to no toxic metabolites. It also replenishes glutathione stores
- Oral dose is 140 mg/kg followed by 70 mg/kg every 4 hrs for three days up to total of 17 doses.
- I/V therapy with NAC is recommended in GI bleeding or obstruction, potential fetal toxicity from maternal toxicity, oral intolerance or when patient is unconscious.

IRON

Children below 5 years of age especially males are more prone to Iron poisoning because of the bright red color of the Iron tablets. In a study from PGI Chandigarh, all the patients had consumed iron tablets given to the mother for anemia prophylaxis.[1] Iron causes corrosive damages to gastrointestinal (GI) mucosa and can lead to acute hemorrhagic gastritis, massive fluid loss (because of third spacing), bleeding and shock. In addition, large amounts of ingested iron overwhelm normal gastrointestinal barriers, resulting in massive iron absorption. When serum iron levels overwhelming the body's binding capacity, free iron produces an increase in reactive oxygen species (ROS) or so called oxygen, free radicals, such as hydroxyl radical, superoxide radical or hydrogen peroxide, leading to lipid peroxidation and cellular membrane damage. It leads to anaerobic metabolism and thus metabolic acidosis. Iron also causes massive post-arteriolar dilatation, increased capillary permeability and coagulopathy leading to severe acidosis and shock, within first few hours. Myocardial failure, caused by ROS induced myocardial damage and other mechanisms, further contribute to shock. Iron affects almost every organ in the body being a systemic intra-cellular poison.

Clinical Features

Clinical effects of Iron occur in four stages described below.

1. Gastrointestinal toxicity (0-3hr) Vomiting, hematemesis, diarrhea, abdominal pain, restlessness, lethargy.
2. Period of apparent stability (Up to 12 hr) Symptoms subside.
3. Mitochondrial toxicity (12-48 hr) Shock, acidosis, coma, seizures, hyperglycemia.
4. Coagulopathy, acute tubular necrosis, hypoglycemia.
5. Hepatic necrosis (> 48 hr) Jaundice, hepatic encephalopathy.
6. Gastric scarring (2-4 weeks) Gastric scarring, gastric/pyloric strictures.

Significant vomiting or diarrhea, shock, coma, iron tablets on abdominal radiograph, coagulopathy, metabolic acidosis (serum bicarbonate <15 mEq/L), hyperglycemia (blood sugar >150 mg/dL) and leucocytosis (TLC >15,000/cumm) all show a high correlation with elevated serum iron. These may be useful indicators of severe toxicity, and help in therapeutic decision-making. If child remains asymptomatic for 6 to 8 hours after ingestion, further intervention is usually not required. Some recommend a desferrioxamine (40-50 mg/Kg, maximum 1 g) challenge test immediately at admission to detect toxic potential while decontamination is being performed. If color of urine becomes 'vin-rose', excess free iron is present. However, a change of urine color to vin-rose is not a consistent finding even if serum iron is >350 µg/dl and it may lead to a delay of 1 to 3 hours.

Management (Flow chart 79.5)

Assessment of severity of toxicity at arrival is done using the following parameters used for include clinical presentation, amount ingested, serum iron levels and total iron binding capacity. The dose of ingested iron can be assessed can be made by the elemental iron content of the specific product as well as its formulation. Histories are usually unreliable. Hence, a child should be assumed to have consumed the higher value of possible ingested dose. A suggested approach to management based on amount of alleged iron ingestion is as follows:

< 20 mg/Kg-Little risk for toxicity. Decontaminate and observe for at least 6 hours.

20-60 mg/Kg-Moderate risk for toxicity. Decontaminate and observe for 6 hours. Consider desferrioxamine chelation therapy.

>60 mg/Kg-High risk for toxicity. Decontaminate and start chelation therapy.

Serum Iron Level

Peak serum iron level usually occurs between 4 and 6 hour of ingestion. A serum iron level more than 350 µg/dL between 2 to 6 hours post-ingestion is said to indicate significant intoxication and levels greater than 500 µg/dL suggest serious risk of severe (Stage III) manifestation. In patients presenting late, a serum iron level less than 350 µg/dL at arrival may not rule out serious intoxication. Another drawback report of serum iron should be available immediately to enable a timely therapeutic decision-making, which is not feasible in most of health care facilities in our country.

Decontamination

Gastric lavage with the largest available tube should be done at the first-contact health care facility if a child has ingested iron in excess of 20 mg/Kg or is symptomatic. After lavage an abdominal radiograph should be obtained to look whether lavage has cleared all the tablets from stomach; if not, lavage should be repeated. Tap water or normal saline is the best lavage solution; bicarbonate, phosphate, magnesium hydroxide or desferrioxamine do not have any proven advantage. At the PICU, gastric lavage must be repeated in all the cases irrespective of their treatment at peripheral health facility.

Whole bowel irrigation (WBI) may benefit children in whom abdominal X-ray reveal tablets beyond the pylorus or throughout the gastrointestinal tract. In situations, where abdominal X-ray is not possible, it is better to give WBI after gastric lavage for rapid and effective cleansing of gut. WBI is also indicated when serum iron level continues to rise despite proven decontamination efforts. For WBI, polyethylene glycol lavage solution (Peglec) may be given through nasogastric tube at rate of 30-40 ml/Kg/hr for 4-8 hours. It will cause diarrhea within 20 minutes and clear effluent will be apparent in as early as 90 minute polyethylene glycol is safe for children and does not cause fluid and electrolyte changes. Alternatively, nasogastric infusion of normal saline (30-40 ml/hr) for 2-3 hours may be used.

Activated charcoal has been used to absorb ingested iron and is likely to be effective especially in ferrous sulfate over-dose but it is not used often because of widely held belief that it binds poorly to iron.

Iron Chelation Therapy

Desferrioxamine (or deferoxamine) is an iron chelator currently available for clinical use as a specific antidote. Each 100 mg of desferrioxamine binds to 9 mg of elemental iron producing ferrioxamine complex, which gets excreted by kidney.

Desferrioxamine is given as continuous intravenous infusion in normal saline at 15 mg/kg/hour (maximum daily dose 360 mg/kg, and total 6 g). A higher rate of infusion may cause hypotension. Stable clinical state of the patient combined with appearance of pinkish (VIN rose) urine indicates response to desferrioxamine, and a serum iron < 100 µg/dL is appropriate end-point.

Desferrioxamine along with exchange transfusion is indicated in patients with free iron level >1000 µg/dl. Patients with renal failure require hemodialysis to remove desferrioxamine-iron complex.

Other chelator therapies are still experimental. Efficacy of orally administered iron chelator deferiprone in acute iron poisoning is still under investigation though findings from experimental studies in animals hold promise for its use in humans. New high molecular weight iron chelator has been produced by coupling desferrioxamine (DFO) to hydroxyethyl starch (HES). Intravenous infusion of this new chelator HES-DFO is well tolerated and produced substantial and prolonged chelation and stimulates urinary iron excretion.

Intensive Care Management

These children should be managed in Pediatric Intensive Care Unit. Initial resuscitative requirement include management of airway, establishment of a venous access and fluid resuscitation using normal saline or Ringer lactate solution. Blood transfusion may be required to replace the blood loss in hematemesis and malena. A severely intoxicated child needs careful monitoring for vital signs, gastrointestinal hemorrhage, fluid intake and output, blood gases and electrolytes. Hemodynamic and respiratory monitoring is helpful in early detection and management of life threatening complications particularly shock. Management of shock requires fluids, a CVP line for continuous assessment of intravascular volume, and inotrops to support failing myocardium. Maintenance of an adequate urine output (>1 ml/kg/hr) is essential to prevent renal failure and to promote excretion of iron-deferoxamine complex. In later stages, some patients may need ventilatory, hepatic and/or renal support. Early liver transplant should be considered in those with hepatic necrosis.

Shock can lead to death in all patients if left untreated. Occurrence of acute liver failure with iron poisoning is associated with high mortality. Patients who died had either shock and/or, acute liver failure and on laboratory investigation a prothrombin Index > 50 percent or acidosis (serum bicarbonate < 12.5 mEq/L). Patients must be carefully followed up for occasional development of gastric scarring and liver fibrosis.

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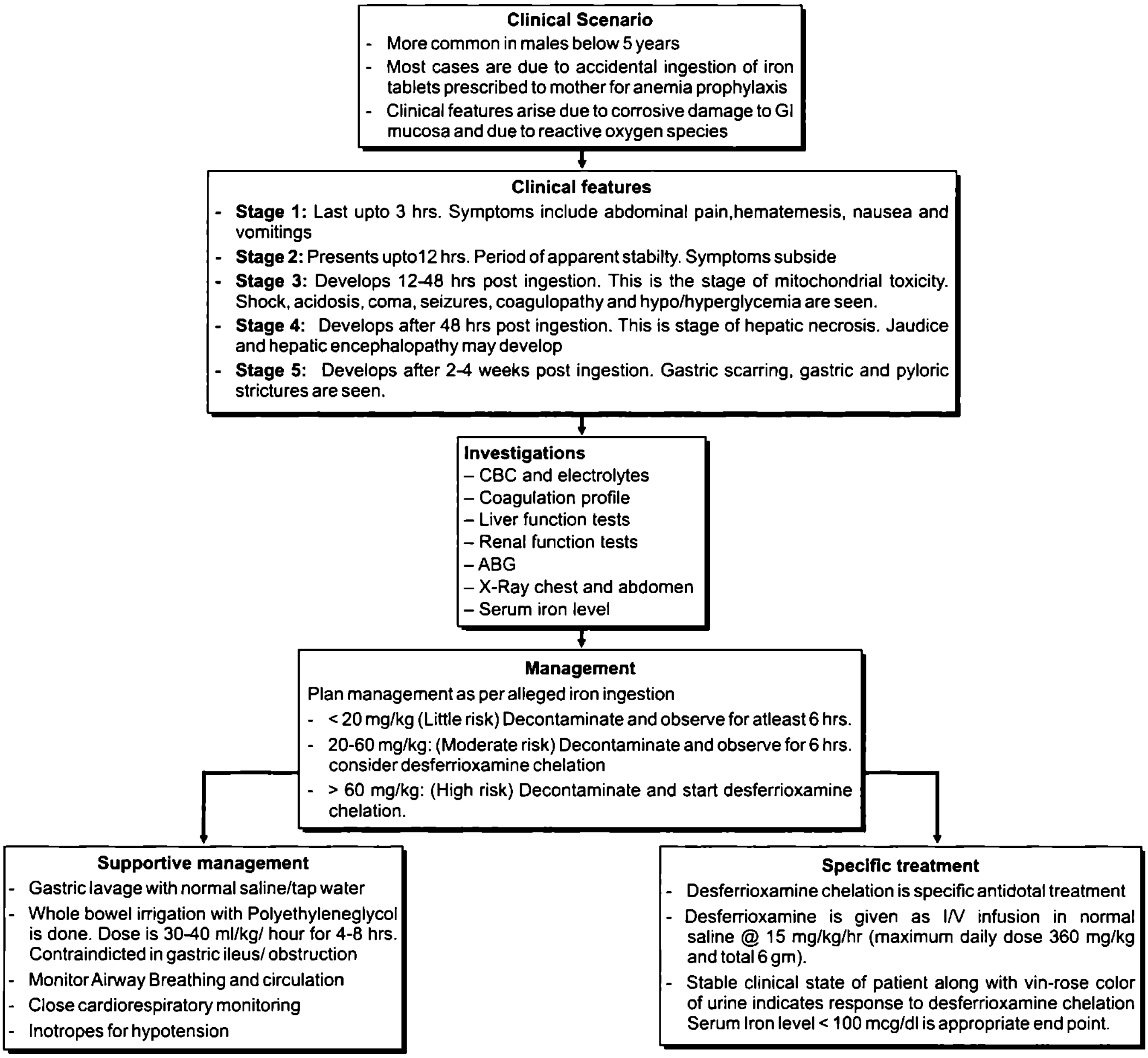
Flow chart 79.5: Iron poisoning



Clinical Scenario

- More common in males below 5 years
- Most cases are due to accidental ingestion of iron tablets prescribed to mother for anemia prophylaxis
- Clinical features arise due to corrosive damage to GI mucosa and due to reactive oxygen species

Clinical features

- **Stage 1:** Last upto 3 hrs. Symptoms include abdominal pain,hematemesis, nausea and vomitings
- **Stage 2:** Presents upto12 hrs. Period of apparent stabilty. Symptoms subside
- **Stage 3:** Develops 12-48 hrs post ingestion. This is the stage of mitochondrial toxicity. Shock, acidosis, coma, seizures, coagulopathy and hypo/hyperglycemia are seen.
- **Stage 4:** Develops after 48 hrs post ingestion. This is stage of hepatic necrosis. Jaudice and hepatic encephalopathy may develop
- **Stage 5:** Develops after 2-4 weeks post ingestion. Gastric scarring, gastric and pyloric strictures are seen.

Investigations

- CBC and electrolytes
- Coagulation profile
- Liver function tests
- Renal function tests
- ABG
- X-Ray chest and abdomen
- Serum iron level

Management

Plan management as per alleged iron ingestion

- < 20 mg/kg (Little risk) Decontaminate and observe for atleast 6 hrs.
- 20-60 mg/kg: (Moderate risk) Decontaminate and observe for 6 hrs. consider desferrioxamine chelation
- > 60 mg/kg: (High risk) Decontaminate and start desferrioxamine chelation.

Supportive management

- Gastric lavage with normal saline/tap water
- Whole bowel irrigation with Polyethyleneglycol is done. Dose is 30-40 ml/kg/ hour for 4-8 hrs. Contraindicted in gastric ileus/ obstruction
- Monitor Airway Breathing and circulation
- Close cardiorespiratory monitoring
- Inotropes for hypotension

Specific treatment

- Desferrioxamine chelation is specific antidotal treatment
- Desferrioxamine is given as I/V infusion in normal saline @ 15 mg/kg/hr (maximum daily dose 360 mg/kg and total 6 gm).
- Stable clinical state of patient along with vin-rose color of urine indicates response to desferrioxamine chelation Serum Iron level < 100 mcg/dl is appropriate end point.

SALICYLATE POISONING

Salicylate poisoning is manifested clinically by disturbances of several organ systems, including the CNS and the cardiovascular, pulmonary, hepatic, renal, and metabolic systems. Salicylates directly or indirectly affect most organ systems in the body by uncoupling oxidative phosphorylation, inhibiting Krebs cycle enzymes, and inhibiting amino acid synthesis.

Clinical Manifestations

Nausea, vomiting, diaphoresis, and tinnitus are the earliest signs and symptoms of salicylate toxicity. Hyperthermia is an indication of severe toxicity.

First phase of the toxicity is characterized by hyperventilation, leading to respiratory alkalosis and compensatory alkaluria. Both potassium and sodium bicarbonate are excreted in the urine. This phase may last as long as 12 hours.

Second phase, paradoxic aciduria in the presence of continued respiratory alkalosis occurs when sufficient potassium has been lost from the kidneys. This phase may begin within hours and may last 12-24 hours.

The third phase includes dehydration, hypokalemia, and progressive metabolic acidosis. This phase may begin 4-6 hours after ingestion in a young infant or 24 hours or more after ingestion in an adolescent.

Investigation

Bedside ferric chloride testing: Qualitative determination for the presence of salicylates can be performed. Positive results with the urine ferric chloride test indicate that obtaining a quantitative serum salicylate level is necessary because even the ingestion of a single aspirin tablet can result in a positive test result.

Arterial blood gas (ABG): Primary respiratory alkalosis may occur, followed by concomitant primary metabolic acidosis resulting from production of lactic acid, metabolites, and other organic acids. Therefore, the most common abnormality is a mixed acid-base disturbance (a primary respiratory alkalosis plus a primary metabolic acidosis).

Salicylate concentration: Initial and serial salicylate levels are important in the evaluation of salicylate toxicity. The absolute level should not detract from the importance of careful and repeated clinical evaluation.

Patients with salicylate concentrations approaching or exceeding 100 mg/dL usually have serious or life-threatening toxicity. A 6-hour salicylate level higher than 100 mg/dL is considered potentially lethal and is an indication for hemodialysis. Chronic ingestion can increase the half-life to longer than 20 hours.

In significant ingestions, serum salicylate levels should be monitored at least every 2 hours until a peak has been reached, then, every 4-6 hours until the peak falls into the nontoxic range.

Serum salicylate levels correlate only moderately with clinical manifestations. In acute ingestion, levels may be high without significant clinical signs. In long-term salicylate toxicity, levels in the high therapeutic range may be associated with significant clinical toxicity.

Treatment (Flow chart 79.6)

The goals of treatment include limiting absorption, enhancing elimination, correcting metabolic abnormalities, and providing supportive care. There is no specific antidote available for salicylates. Gastric lavage and activated charcoal are useful for acute ingestions but not in cases of chronic salicylism. Patients with chronic rather than acute ingestions of salicylates are more likely to develop toxicity, especially of the CNS, and require intensive care.

Gastrointestinal Tract Decontamination

Initial treatment should include the use of oral activated charcoal; use of cathartics is not indicated with activated charcoal.

Repeated doses of charcoal may enhance salicylate elimination and shorten the serum half-life. WBI was more effective in reducing absorption. When enteric-coated aspirin has been ingested or salicylate levels are not decreasing despite treatment with charcoal, WBI should probably be used in addition to charcoal therapy.

Urinary Alkalinization

Renal excretion of salicylic acid depends on urinary pH. Increasing the urine pH to 7.5 prevents reabsorption of salicylic acid from the urine. Since acidosis facilitates transfer of salicylate into tissues, especially in the brain, it must be treated aggressively by raising blood pH higher than brain pH, thereby shifting the equilibrium from the tissues to the plasma.

Concomitant alkalinization of blood and urine keeps salicylates away from brain tissue and in the blood, in addition to enhancing urinary excretion. When the urine pH increases to 8 from 5, renal clearance of salicylate increases 10-20 times.

Hypokalemia and dehydration limit the effectiveness of urine alkalization. Hypokalemia prevents excretion of alkaline urine by promoting distal tubular potassium reabsorption in exchange for hydrogen ions. Symptomatic patients typically have low serum potassium concentrations or serum potassium concentrations low in the reference range. Treatment with sodium bicarbonate alone may produce further intracellular shift of potassium ions, which further impairs the ability to excrete alkaline urine. Repletion of potassium is often necessary, even when serum potassium levels are in the low reference range (e.g. < 4.5 mEq/L).

Urinary alkalization should be continued at least until serum salicylate levels decrease upto the therapeutic range (< 30 mg/dL).

Hemodialysis

Indications for hemodialysis include a serum level greater than 120 mg/dL (acutely) or greater than 100 mg/dL (6 h postingestion), refractory acidosis, coma or seizures, non-cardiogenic pulmonary edema, volume overload, and renal failure.

In chronic overdose, hemodialysis may be required for a symptomatic patient with a serum salicylate level greater than 60 mg/dL.

Although hemoperfusion has a slightly higher rate of drug clearance than hemodialysis, dialysis is recommended because of its ability both to correct for fluid and electrolyte disorders and to remove salicylates.

Peritoneal dialysis is only 10-25 percent as efficient as hemoperfusion or hemodialysis and not even as efficient as renal excretion.

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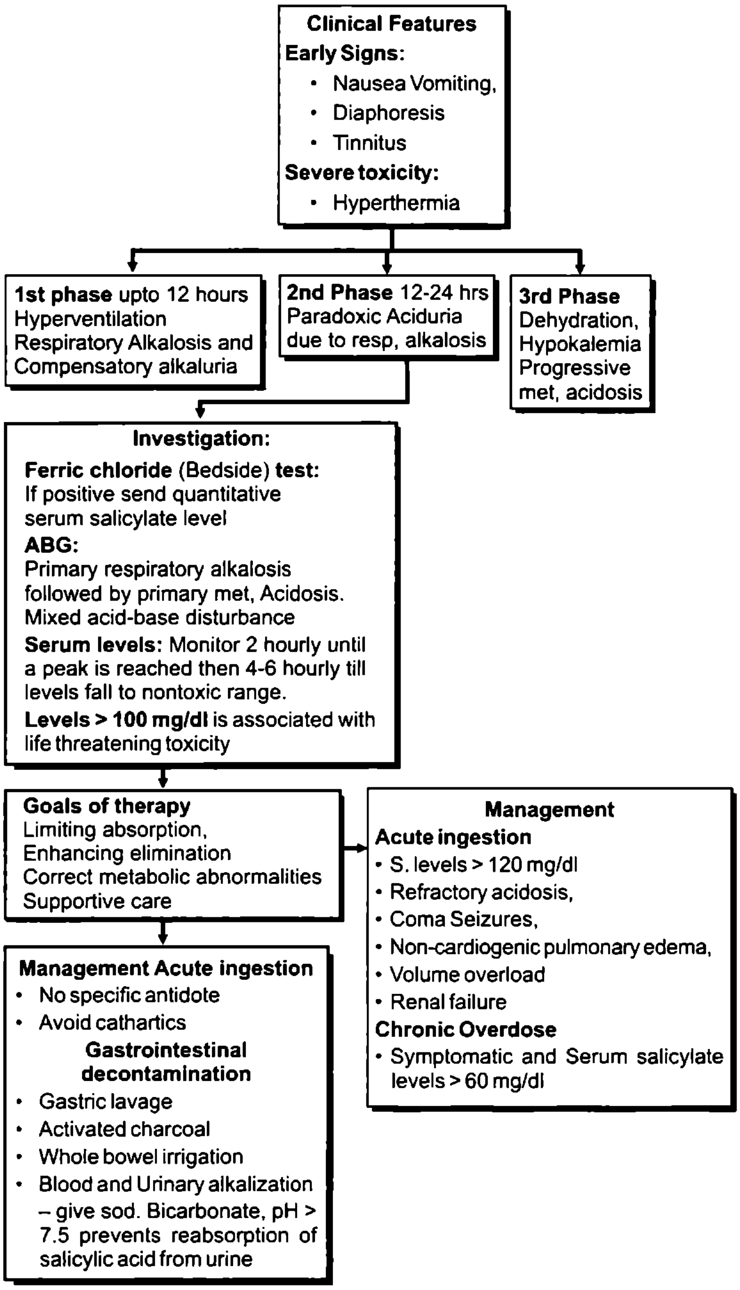
Flow chart 79.6: Salicylate poisoning



Clinical Features
Early Signs:
- Nausea Vomiting,
- Diaphoresis
- Tinnitus

Severe toxicity:
- Hyperthermia

1st phase upto 12 hours
Hyperventilation
Respiratory Alkalosis and
Compensatory alkaluria

2nd Phase 12-24 hrs
Paradoxic Aciduria
due to resp, alkalosis

3rd Phase
Dehydration,
Hypokalemia
Progressive
met, acidosis

Investigation:

Ferric chloride (Bedside) **test:** If positive send quantitative serum salicylate level

ABG: Primary respiratory alkalosis followed by primary met, Acidosis. Mixed acid-base disturbance

Serum levels: Monitor 2 hourly until a peak is reached then 4-6 hourly till levels fall to nontoxic range.

Levels > 100 mg/dl is associated with life threatening toxicity

Goals of therapy
Limiting absorption,
Enhancing elimination
Correct metabolic abnormalities
Supportive care

Management
Acute ingestion
- S. levels > 120 mg/dl
- Refractory acidosis,
- Coma Seizures,
- Non-cardiogenic pulmonary edema,
- Volume overload
- Renal failure

Chronic Overdose
- Symptomatic and Serum salicylate levels > 60 mg/dl

Management Acute ingestion
- No specific antidote
- Avoid cathartics

Gastrointestinal decontamination
- Gastric lavage
- Activated charcoal
- Whole bowel irrigation
- Blood and Urinary alkalization – give sod. Bicarbonate, pH > 7.5 prevents reabsorption of salicylic acid from urine

METHANOL AND ETHYLENE GLYCOL

Methanol is metabolized to formaldehyde further metabolized to formic acid. Toxicity is caused by formic acid. Early manifestations after ingestion include drowsiness, mild inebriation, and gastric irritation, including nausea and vomiting. The onset of serious effects, including profound metabolic acidosis and visual disturbances, is delayed upto 24 hours. Pupils may be dilated and unreactive to light, and retinal edema and optic disc hyperemia may be noted. Visual disturbances are usually reversible, but in significant poisonings, blindness has occasionally been permanent. An anion-gap metabolic acidosis develops; thus, serum electrolytes, pH, and acid-base balance should be monitored. It is commonly used in windshield washer fluids, fuel additives, liquid fuel canisters, and industrial solvents. Ethylene glycol is commonly found in antifreeze solutions for car radiator.

Ethylene glycol is metabolized to glycoaldehyde further converted to glycolic acid. Glycolic acid is metabolized to glyoxylic acid and oxalic acid, which cause toxicity. Oxalic acid combines with serum and tissue calcium, causing hypocalcemia and the formation of calcium oxalate crystals. Early symptoms occur 1-12 hours after ingestion and include gastric irritation, with nausea and vomiting, and CNS effects, including drowsiness and inebriation. Metabolic acidosis begins to develop. From 12-24 hours after ingestion, cardiac dysrhythmias, muscle pain, and tetany due to hypocalcemia may occur. Later in the clinical course, cardiac failure, seizures, cerebral edema, and renal failure occur. Renal failure is caused by the deposition of calcium oxalate crystals in renal tubules.

Treatment

Because methanol and ethylene glycol are rapidly absorbed, gastric decontamination is usually not of value. Activated charcoal does not bind either agent. Metabolic acidosis is treated with intravenous sodium bicarbonate at doses of 1-2 mEq/kg.

Ethanol is an antidote for both methanol and ethylene glycol poisoning because it is preferentially metabolized over methanol and ethylene glycol by alcohol dehydrogenase, thus preventing formation of toxic metabolites. Fomepizole is a potent competitive inhibitor of alcohol dehydrogenase that has been approved for use in both methanol and ethylene glycol poisoning. There is limited experience with this agent in children. Hemodialysis effectively removes ethylene glycol, methanol, and their acid metabolites. It is also useful for correcting severe metabolic acidosis. The indications for hemodialysis are refractory metabolic acidosis, renal failure, or ethylene glycol or methanol blood levels exceeding 50 mg/dL.

CALCIUM CHANNEL BLOCKERS

Calcium channel blockers encompass a variety of chemical structures that produce various effects on the myocardium and the systemic vasculature. The toxic effects of these drugs are an extension of their therapeutic effect. In overdose, either cardiac dysrhythmias or hypotension may occur or both effects may be seen. Bradycardia and varying degrees of atrio-ventricular block are common. Hypotension develops secondary to dilation of vascular smooth muscle. Myocardial depression may lead to shock in severe cases. Careful blood pressure and electrocardiographic monitoring and serial serum glucose measurements should be followed.

Treatment

After appropriate supportive care has been instituted, absorption should be prevented using activated charcoal if appropriate. Whole bowel irrigation should be considered if a sustained-release product has been ingested. Bradycardia and conduction disturbances require the placement of a pacemaker. Hypotension may be treated with fluids and vasopressors. Intravenous calcium may reverse myocardial depression. Calcium chloride is preferred over calcium gluconate because it contains a greater amount of calcium per gram. Because the duration of action of calcium salts is much shorter than that of calcium channel blockers, administration by continuous infusion may be necessary.

ANTIDEPRESSANTS

TRICYCLIC ANTIDEPRESSANTS

The tricyclic antidepressants (TCAs) and the selective serotonin reuptake inhibitors (SSRIs) represent the two most common classes of antidepressants of toxicologic significance.

Clinical features: Drowsiness, lethargy, or coma has been reported in as many as one third of pediatric cases. Coma, when it occurs, usually resolves in a few hours, but may last longer than 24 hr. Hypertension may occur soon after ingestion but rarely requires treatment. Hypotension is uncommon but is a poor prognostic sign. Other cardiac findings include slowing of myocardial conduction, multifocal premature ventricular contractions, and ventricular tachycardia, flutter, or fibrillation. In addition to widening of the QRS complex, QT prolongation occurs with T-wave flattening or inversion, ST segment depression, right bundle branch block, and complete heart block. Hypoventilation with respiratory arrest may occur without warning. The electrocardiogram (ECG) should be closely monitored for QRS widening and QT and QTc prolongation. QRS duration and axis deviation and the level of consciousness have been suggested as predictors of potential toxicity.

Treatment: After general life support measures are instituted, including endotracheal intubation if indicated, efforts should be made to prevent absorption. Emesis is contraindicated. Activated charcoal should be administered. Sodium bicarbonate in doses sufficient to achieve a serum pH of 7.45-7.55 should be administered to treat and prevent dysrhythmias. Lidocaine is used to treat dysrhythmias that are unresponsive to serum alkalization. Hypotension may respond to standard fluid therapy, although vasopressors such as norepinephrine may be required. Asymptomatic children should be observed and the ECG monitored for at least 6 hr after exposure. If any manifestations of toxicity (e.g., a QRS interval > 0.10 msec, conduction defects, altered mental status, hypotension, or hypoventilation) develop, continue monitoring in an intensive care unit for 24 hours. Only completely asymptomatic children should be discharged after 6 hours of observation.

CARBON MONOXIDE POISONING

CO is a colorless, odorless gas produced during the combustion of any carbon-containing fuel. CO binds to hemoglobin, displacing oxygen, with an affinity for hemoglobin that is about 250 times that of oxygen. Next, CO impairs the ability of hemoglobin to release oxygen to tissues. Finally, CO also binds to cytochrome oxidase in tissues, impeding oxygen utilization resulting in tissue hypoxia. Children may experience syncopal episodes as a first symptom. Neurologic manifestations of visual acuity and field deficits, confusion, and focal motor weaknesses may be observed. At high concentrations, coma, seizures, respiratory instability, and death may occur. Cerebral computed tomography reveals focal infarctions. Cortical lesions may be evident on magnetic resonance imaging.

In addition to general supportive care, treatment of CO poisoning requires the administration of high concentrations of oxygen. Hyperbaric oxygen is useful. High concentrations of oxygen shorten the half-life of CO in the blood and tissues. Severely poisoned patients benefit from hyperbaric oxygen therapy.

SMOKE INHALATIONAL INJURY AND CARBON MONOXIDE POISONING

Commonest cause of carbon monoxide poisoning is smoke inhalational injury. Therefore, in this section we shall discuss other injuries associated with smoke inhalational injury in addition to carbon monoxide (CO) poisoning.

- Smoke inhalational injury
- Three most common injuries occur with smoke.
    - Thermal injury
    - Asphyxia
    - Carbon monoxide poisoning

Thirty to fifty percent of children involved in burns accidents suffer inhalational injury, contributing to 50 to 80 percent mortality in burn victims.

Smoke injury exposes the child to thermal injury, chemical asphyxia and carbon monoxide poisoning.

Thermal Injury

Thermal injury from smoke inhalation is usually limited to upper airway as it cools the hot air by the time it gets to glottic area, lower airway is protected by reflex laryngospasm and closure of the glottic opening. Significant lower airway injury occurs with steam which is much hotter than dry air. Smoke inhalation can cause airway edema fairly rapidly. Therefore, in unconscious victims, patients with burns to lips and nose, soot in mouth or nose, stridor or hoarseness, early tracheal intubation may be lifesaving. In patients with florid airway edema, fiberoptic bronchoscopy may facilitate examination of the airway and endotracheal intubation.

Asphyxia

In enclosed space fires, oxygen concentration may drop to < 5 percent due to occupancy by smoke leading to asphyxia. This is further aggravated by tissue hypoxia caused by carbon monoxide and cyanide toxicity reducing oxygen capacity and utilization. This further disables the individuals capacity to escape from the area on fire leading to mortality, even though surface burns may not be that significant.

Carbon Monoxide Poisoning

Fifty percent of autopsies performed on fire victims reveal lethal concentrations of carboxyhemoglobin (COHb). Sources of CO include indoor kerosene, smoke in enclosed space burns, and methylene chloride ($CHCl_2$) which is main component in paint removers metabolizing to CO.

Mechanism of Toxicity

CO has 240 times binding affinity to Hb compared to oxygen.

P50 (the partial pressure at which Hb is 50 percent saturated) for CO is 0.10 mmHg and for oxygen it is 27 mmHg.

CO causes oxyhemoglobin dissociation curve to be shifted to left (tight binding) impending release of oxygen in tissues from blood. CO also binds to cytochrome oxidase causing cytotoxic hypoxia. This action is most toxic leading to metabolic acidosis due to impaired oxygen utilization by mitochondria.

Clinical Effects

Multiorgan failure syndrome will result as a result of tissue hypoxia.

Cerebral edema, pulmonary edema, coronary ischemia, myoglobinuria and acute renal failure, cutaneous blisters, blindness, vestibular dysfunction leading to tinnitus, nystagmus, ataxia, increased serum amylase, hyper-uricemia, microangiopathic hemolytic anemia, thrombotic thrombocytopenic purpura can occur.

Pregnant women involved in CO exposure had neurological sequelae in newborns.

Diagnosis

One has to suspect CO poisoning based on history. Blood gas oxygen saturation may be 100 percent due to estimates on nomograms. Based on partial pressure, pulse oximetry will be normal because COHb is sensed as oxyhemoglobin, however, CO oximetry saturations will be low. Measurement of COHb levels is important. Symptoms are as follows based on COHb levels.

- < 10 percent shortness of breath with vigorous exertion
- < 20 percent headaches
- 30-50 percent irritability, nausea, dizziness, confusion, blurring of vision and fainting on exertion
- > 50 percent unconsciousness and convulsions
- 60-80 percent fatal

Management

Definitive therapy is oxygen. It dissociates CO from COHb and also increases dissolved oxygen in plasma.

Management in the PICU remains symptomatic and supportive. Aggressive unconsciuos child should be placed on hemodynamic support with mechanical ventilation with 100 percent oxygen. Hyperbaric oxygen may also be tried if COHb is more than 25 percent (rationale being to increase the amount of dissolved oxygen in plasma). Hundred percent oxygen with three atmospheres for one hour followed by two atmospheres for two hours until COHb level falls below 10 percent.

Mannitol and mild hyperventilation is useful. Mild acidosis is beneficial for oxygen release by rightward shift of oxyhemoglobin dissociation curve.

Cyanide Toxicity

Hydrogen cyanide is present in smoke. CO and cyanide toxicity usually coexist causing worse tissue hypoxia. Wool, silk, nylon decompose to produce cyanide. Blood cyanide levels are high (> 1 mg/l). This test is not easily available.

Patients in ICU receiving nitroprusside are also at risk of cyanide toxicity. Sodium nitrite and or sodium thiosulphate is treatment of choice in addition to supportive management.

Lastly pulmonary inhalational injury that frequently presents as pulmonary edema and chemical acute respiratory distress syndrome (ARDS) needs to be treated on same line as ARDS.

SUMMARY

In all burn victims, smoke injury must be suspected. In patients with oral burns, soot in mouth, stridor airway must be secured to prevent fatality. CO poisoning is diagnosed by high suspicion. Cerebral and pulmonary edema, in combination with coronary ischemia can be lethal. Aggressive supportive management is the key to survival. Hyperbaric oxygen should be considered if COHb level are higher than 25 percent. Sodium nitrite and sodium thiosulphate should be administered if no improvement is seen.

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ALUMINIUM PHOSPHIDE POISONING

Aluminium phosphide is a major suicidal agent in India and developing countries and may be ingested accidentally by children.[1-3] In India it is freely available as a fumigant insecticide to preserve stored food grains. It is highly toxic to the heart lungs and blood vessels causing profound shock, ARDS and pulmonary edema and profound hypoxemia and cardiac failure. In India children have been given the poison by their parents who subsequently consume it themselves with suicidal intentions.

Epidemiology

In 559 consecutive patients of poisoning, Aluminium phosphide poisoning accounted for 1-16 percent of admissions.[4] Males out numbered females 2:1. Seventy-eight percent of patients were in the age of 15-30 years. More than 70 percent were of the lower socio-economic group. Majority (> 90%) of poisoning were suicidal. Marital disharmony accounted for one-third of the cases.

Mode of Action

The acute effects of the drug depends on the route of exposure.

If exposed via the lungs the toxin will be inhaled in the form of phosphine gas. This results in pulmonary edema and hypoxia. Later it interferes with cellular oxygenation throughout the body causing multiple organ dysfunction syndrome (MODS). If ingested, aluminium phosphide is converted to phosphine in the body by contact with water.

If exposure is through the skin or eyes burning from phosphorus gas can cause chemical burns in the eyes and skin.

Structure and Reactions

Aluminium phosphide reacts with water forming phosphine gas which then forms phophoric acid in the presence of water. Phosphine gas and phosphoric acid are toxic. Silver nitrate test paper reacts with phosphine and it is used chemically for diagnosis.

Mechanism of Action

The exact mechanism is still uncertain.[5] It is believed to be a competitive inhibitor of cytochrome oxidase or to act directly liberating free oxygen radicals. It, thus, causes uncoupling of oxidative phosphorylation and leads to profound cellular hypoxia.

Clinical Presentation

Systemic Effects

Cardiovascular Profound cardiovascular effects may occur, cardiac dysrhythmias (atrial and ventricular tachydysrhythmias, AV blocks) ST depression, severe impairment of myocardial contractility, and intractable shock are the usual presentation in severe cases.[6] Autopsy studies have revealed toxic myocarditis presumably due to a direct myocardial injury by phosphine.[7,8]

Pulmonary: Pulmonary edema due to severe heart failure and ARDS due to direct effects of the toxic or severe cellular hypoxia occurs in most severe cases.

In majority of cases, rapidly progressive cardiovascular collapse or severe ARDS occurs and there is rarely enough time for MODS to occur.

Gastrointestinal, vomiting, abdominal pain and diarrhea, hepatic failure occur late as a part of the MODS.

The overall mortality is reported to be 80-100 percent.[4] Those who survive often do so because of loss of potency of the compound due to exposure of the tablets to air. The freshness of the tablets thus have a major impact on the mortality rate. When fresh, the fatal dose for a 70 kg adult is 0.5 gm (one-sixth of the available 3 gm tablet. Chugh et al.[9] showed that mortality was only 2.5 percent in patients who have consumed fully exposed tablets.

Diagnosis

Diagnosis is made by the high index of suspicion and a careful history. A positive silver nitrate test in breath and/or gastric aspirate is definitive.[10] The gastric lavage may have the characteristic fishy smell.

Management in the Pediatric Intensive Care Unit

General mangement principles of pediatric cardiovascular collapse and ARDS apply. There is no specific antidote to this poisoning. A gastric lavage should always be undertaken. Management involves aggressive supportive therapy for severe cases including Mechanical Ventilation and hemodynamic support.[11] Survival have been reported following aggressive volume resuscitation, vasopressor (Noradrenaline, Dopamine) and inotropic support (Dobutamine, Amrinone).[11] The use of magnesium sulphate is controversial.[12,13] It may act as an antioxidant affording protection to the tissues from phosphine.[14] However, many have questioned the rationale of its administration as hypermagnesemia is demonstrable in many cases.[15] Many have shown no efficacy of magnesium infusion in reducing mortality. In fact, it may be detrimental as it has hypotensive action. Therefore, the mainstay of management remains aggressive hemodynamic support.

Prevention

The medical community has raised the issue of restricting uncontrolled sale of the pesticide at various fora. The magnitude of suicidal aluminium phosphide poisoning has assumed epidemic proportions and requires urgent administrative action.[16] As a safety measure, insecticides should be stored away from the reach of young children.

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POISONING BITES

Snake Bite

Snakes belong to three major families 1. Elapidae (Common Cobra, King Cobra and Krait). 2. Viperidae (Russell's viper, Pit viper and Saw scaled Viper) 3. Hydrophidae (Sea Snakes). Although there are about 330 species snakes in India out only about 70 species are poisonous, most of the morbidity and mortality seen clinically are due to 5 species. King Cobra (Ophiophagus hennah), Common Cobra (Naja Naja), Russell's Viper (Daboia rusellii), Krait (Bungarus caeruleus) and Saw scaled Viper (Echis carinatus). Exact data is unavailable as significant number of snake bite victims first consults traditional healers. All over India about 10,000 – 15,000 deaths occur due to snake bites annually in India. Highest incidence is seen between evening and midnight. There is also a seasonal pattern seen because rainfall and temperature compel snakes to come out of their shelter. Epidemics of snake bites can occur in relation to floods. Most commonly bites are seen on lower extremities.

Pathophysiology

Snake venom is a complex mixture of various substances like enzymatic and nonenzymatic compounds. Enzymes identified in snake venom include phospholipases, phosphatases, proteases, hydrolases, nucleosidases, nucleotidases, esterases, hyaluronidases and acetyl-cholinesterases.[1] The non-enzymatic compounds are neurotoxins and hemorrhagins. There is preponderance of particular toxin in particular species, which is the basis of clinical classification of bites into neurotoxic, hemotoxic and myotoxic. Even within a single species, there is considerable difference in composition of venom depending upon its geographical distribution. Hence snake antivenom prepared from snake venom of a particular locality would be more useful than that prepared from venom of snakes in different geographical area.

Clinical Features

Time of onset of systemic effects of envenomation is quite variable, i.e. from few minutes to few hours. Therefore asymptomatic patients with evidence of snake bite should be kept under observation for 24 hours. Sea snakes always produce myotoxic effects within 2 hours of bite.

Local changes are the earliest manifestations of snake bite usually seen within 30 minutes (with two exceptions i.e. emotional effects and Krait bites). Local manifestations are minimal or absent in Krait bites. Cobra bites have significant local effects limited to area of bite while local effects of Viper bites are extremely pronounced extending much beyond site of bite, even upto trunk. Various local effects seen are pain, wheal, edema, bullae (blood filled in Viper bites), paraesthesia, local bleeding (mainly in Vipers), necrosis and gangrene. Regional lymphadenopathy is also seen which an early and reliable sign of systemic envenomation.

Local effects caused by snake bites are due to the effect of the venom and to secondary bacterial infection of the wound. Local effects of snake bite can be very devastating and may lead to loss of limb due to necrosis and gangrene.

Fang marks are seen as two puncture wounds few millimeters to 4 cm apart. If fang marks are not easily seen they should be looked using magnifying glass. The Bailey's method consists of injecting 2 percent xylocaine through fine needle and observing the sites of oozing.[5] Though Krait bites are painless, local paresthesias, heaviness and pricking sensation may be reported by the patient.

Systemic Effects Snake Evenomation

The most common and early effects following snake bite is the strong emotional response of the victim including intense fear of death, manifested by sweating, vomiting, tremors, etc. Hyperventillation due to anxiety may result into tingling numbness in extremities, tetany and dizziness. Some may develop syncope with bradycardia and sweating.

Neurotoxicity: is commonly seen after Cobra and Krait bites. Neurological effects are due to selective d-tubocurarine like neuromuscular blockade, which results into flaccid paralysis of muscles. Muscles innervated by cranial nerves are affected first. Ptosis is the earliest manifestation followed by external ophthalmoplegia. Progressive paralysis involves muscles of palate, jaw, tongue, larynx, neck and muscles of deglutition. Pupils remain reactive to light till terminal stages. Muscles of chest including diaphragm are involved late. Deep tendon jerks are preserved till late stages. Bulbar paralysis causes accumulation of secretions in mouth due to dysphagia. Neurotoxic snake bite patients may be wrongly assumed to be comatose due to their closed eyes (external ophthalmoplegia and ptosis), inability to speak (bulbar paralysis) and inability to move limbs (flaccid paralysis). Paralysis usually lasts for 2 days and then recovers over next 2 to 5 days.

Coagulopathy: Effects on coagulation system are usually seen with viper bites. Important effects are intravascular coagulation (resulting in consumption coagulopathy or DIC) and intravascular hemolysis. Bleeding from fang marks, blood filled bullae are seen locally. Other manifestations seen are bleeding gums, GIT bleeding, bleeding from injection sites, epistaxis, intracranial bleeds, etc. Although various snake species can lead to acute renal failure, it is quite common with viper bites.

The Whole blood clotting test is a simple, bedside test and very informative test requiring only a dry, clean and new glass test tube. Take 2 to 5 ml blood in test tube and leave it undisturbed for 20 minutes. Tilt the test tube once after 20 minutes to see if blood is still liquid which will indicate onset of consumption coagulopathy and is diagnostic of viper bite. WBCT is also used to assess effectiveness of ASV and controlling its administration. It is done on admission and then every 6 hours.

These are reported with Viper and Cobra bites. Cardiotoxic manifestations include tachycardia, hypotension, arrhythmia, hyperkalemic cardiac arrest, myocardial infarction etc. Myotoxic effects are mainly seen with sea snake bites. Muscle necrosis can lead to myoglobinuria. Early manifestations are generalized pain, tenderness, stiffness of muscles and trismus. Sometimes hemorrhagic and neurotoxic effects were seen as late as one week after snake bite. Possible explanation for this was a local bleb, which acted as venom depot (and was inaccessible to antivenom), specially when the wound was handled surgically. Due to the ongoing absorption of venom from the blood, having half life of 26 to 95 hrs, signs of systemic envenomation may be seen hours or even days after initially good response to antivenom. Thus daily evaluation of patient for 3 to 4 days is recommended. Local effects resulting in gangrene, pituitary hemorrhage resulting into hypopituitarism are some of the long term effects seen.

Envenomation without bite is seen with spitting Cobra (Naja nigricollis) which can eject venom from a distance of 6 to 8 feet. The venom is usually aimed at victims eyes and can result in conjunctivitis, corneal ulceration, anterior uveitis and hypopyon needing enucleation. Bite by killed snake may occur because the biting reflex is preserved in recently killed snake or in severed heads. Thus one should not handle them and should take extreme caution while transporting them. Snake bite to lactating mother. Breast feeding should be continued in such cases.

Factors which Indicate Poor Prognosis

1. Children are at greater risk of mortality and morbidity due to higher amount of venom injected per kilogram body weight.
2. Site of bite: Patients bitten on trunk, face and directly into bloodstream have worse prognosis.[6]
3. Movement and exertion following bites result into more systemic absorption of venom. This could result out of panic or initial asymptomatic period during which patient might walk to health care facility.
4. Snake bites through clothing or boots offer considerable protection as aperture for venom flow is not at the tip of fangs but a little proximal to it.
5. Time elapsed between snake bite and administration of antivenom is also an important prognostic factor.
6. In a study from India vomiting, neurotoxicity and raised serum creatinine were reported to be significant predictors of mortality among inpatients with snake bite.[9]

Identifying Common Venomous Snakes of India

Snakes	*Characteristics*	*Clinical features*
Cobra	Hood bearing spectacle, white band between hood and body	Local signs + neurotoxic
Krait	Blue colored, white band across back Bites people sleeping on the floor,	No local signs + neurotoxic
Russell's Viper	Triangular head, white V mark, spots on body, hissing sound	Triangular head, white V mark, spots on body, hissing sound
Saw Scaled Viper	White mark on head like bird's footprint or an arrow	No local signs + myotoxic

Investigations

1. Blood counts reveals anemia, polymorphonuclear leukocytosis (indicator of systemic envenomation).
2. Signs of hemolysis and DIC on peripheral smear may be seen in Viperine bites.
3. Coagulation profile with prolonged clotting time and prothrombin time, hypofibrinogenemia, fibrin degradation products are deranged.
4. Renal profile and serum electrolytes real uremia and hyperkalemia.
5. Urine examination may reveal hematuria, proteinuria, hemoglobinuria and myoglobinuria.
6. ECG changes like bradycardia, A-V block, ST segment elevation or depression, T wave inversion, QT prolongation, signs of hyperkalemia and changes suggestive of acute anterior wall myocardial infarction may be seen.
7. Grouping and cross matching samples should be obtained.

Management (Flow chart 79.7)

Pre-hospital Management (First aid)

In India there is a widespread belief in traditional healers and medicines which do more harm than good. Treatments that should be avoided include incision over bite marks, suction of venom and local ice packs are discouraged. First aid methods with unequivocal benefit are reassurance, immobilization of bitten part and tourniquet. Tourniquet should be used only in Krait bites and not in Cobra or Viper bites where it will increase local complications. Tourniquet should be one to four inch broad (preferably elastic crepe bandage) applied proximal to Krait bite loose enough to pass one finger below it and distal pulses be well felt. It should be removed only after patient receives antivenom.

Immobilization of bitten part with sling or splint is very important as muscular contraction increases venom absorption into blood steam and lymphatics.[8] Avoid any interference with the bite wound as this may introduce infection, increase venom absorption and increase the chance of local bleeding. The patient should be kept in lateral decubitus position to avoid aspiration and the bitten part should be maintained below the heart level.

Rapid Assessment and Resuscitation in the Emergency Ward

Once in hospital, rapid assessment of airway, breathing and circulation should be done. Administration of oxygen, establishment of intravascular access and cardiopulmonary resuscitation started as per the need. Some common situations needing urgent resuscitation include profound hypotension, shock, respiratory failure, hyperkalemic cardiac arrest etc. Repeated cardio respiratory assessment helps detect respiratory and cardiac failure early. Mechanical ventilation is indicated for respiratory paralysis in cases of neurotoxicity by Cobra and Krait, this form of therapy is life saving. Even when no ASV is available, mechanical ventilation alone can save life of neurotoxic snake bite victim leading to respiratory paralysis. In fact in such cases, antivenom alone cannot be relied upon to prevent death from respiratory paralysis. Artificial ventilation is must in them.

Anti Snake Venom (ASV)

Indications

All snake bites do not need antivenom and as it has potential side effects, costly and has limited availability, it should be judiciously used only in cases with evidence of envenomation. Anti snake venom administration is indicated only in the presence of signs local or systemic envenomation. Even minimal and nonprogressive local edema appearing after two hours of bite is not an indication for ASV.

Indications for ASV for Local Envenomation

1. Local swelling involving more than half of bitten limb (in absence of tourniquet).
2. Swelling after bites on digits (toes and fingers).
3. Rapid extension of swelling (e.g. beyond wrist or ankle within few hours of bites on hands or foot).
4. Enlarged tender regional lymph nodes.

Indications for ASV for Systemic Envenomation

1. Hemostatic abnormalities: Spontaneous clinical bleeding, 20 WBCT or other laboratory evidence of coagulopathy or thrombocytopenia (<1,00,000/cumm).

2. Neurotoxic signs: Ptosis, external ophthalmoplegia, flaccid paralysis, heavy eyes, bulbar paralysis, etc.
3. Cardiovascular abnormalities: Shock, arrhythmia or ECG abnormalities.
4. Acute renal failure.
5. Hemoglobinuria, myoglobinuria or evidence of intravascular hemolysis.
6. Supporting laboratory evidence of systemic envenomation like early polymorphonuclear leucocytosis.
7. Vomiting, headache, inappropriate drowsiness etc.

Anti snake venom is available as a freeze dried powder, which is reconstituted with the diluent (10 ml). It is always administered. The dose of ASV is same for adult and a child, a single dose is usually sufficient for Cobra and Krait bites. Viper bites may need multiple doses. Ten vials are dissolved in 200 ml normal saline and infused over one hour. Thereafter 5 vials are given over next 24 hours. Maximum dose needed is 30 vials for neurotoxic and 45 vials for coagulopathy effects. ASV should be administered as early as possible once signs of envenomation are seen. Best effects are observed when it is given within 4 hours of bite but is useful in symptomatic patients even upto one week after the bite and in case of hemostatic abnormalities even upto two or more weeks.

Sensitivity Testing

0.1 ml of the ASV is diluted in 1 ml diluent to obtain a 1:10 dilution and injected subcutaneously. The patient is closely observed for half to one hour for development of local or generalized hypersensitivity reactions. Adrenaline should always be kept ready. Sometimes pretreatment with antihistaminics (both anti H_1 and anti H_2) and corticosteroids may be used in high risk cases.

ASV is not useful for preventing local tissue necrosis. Also neurological manifestations at the presentation, which are due to venom already attached to receptors, are not going to respond to ASV. This is because ASV will neutralize venom in circulation before getting attached to receptors. Hence monitoring of neurological signs present in the patient before administration of ASV should not be used to judge the response to ASV.

Neostigmine

It is useful for neuromuscular junction blockade caused by neurotoxic snake bites. It is useful only for postsynaptic type of blockade (occurring with Cobra bites) and not for presynaptic block (Krait bites cause both pre and postsynaptic blockade). Edrophonium test can predict usefulness of neostigmine but it is not available in India. Hence response to first dose of neostigmine is useful. Dose is 25 to 50 microgram/kg 4 hourly till complete neurological recovery. It is to be given with atropine.

Local Wound Management

The wound should be cleaned thoroughly and kept open, if there is significant swelling or tenderness in the proximal edge of the swelling it should be marked with ink so that its progression can be monitored. Hourly progression of edema is recorded by measuring the circumference of the bitten limb. Wound debridement is often required on the 3rd or 5th day. If compartment syndrome occurs it is managed by fasciotomy.

Other Supportive Measures

1. Avoid Intramuscular injections.
2. Prophylactic antibiotics are not recommended for all snake bites. For patients in whom infection at bite site is suspected antibiotics to cover gram positive, gram negative and anaerobes should be given, e.g. Penicillin + B lactamase inhibitor, metronidazole or clindamycin.
3. A booster dose of tetanus toxoid is advised.
4. Blood transfusion, blood components, volume expanders, peritoneal dialysis are needed depending on clinical situation. Blood products are usually not helpful till there is circulating venom in victims body. In fact, they can do more harm by adding substrates for unneutralised venom. Hence ASV is the mainstay of treatment.
5. Acute renal failure is managed conservatively, occasionally peritoneal dialysis may be necessary.

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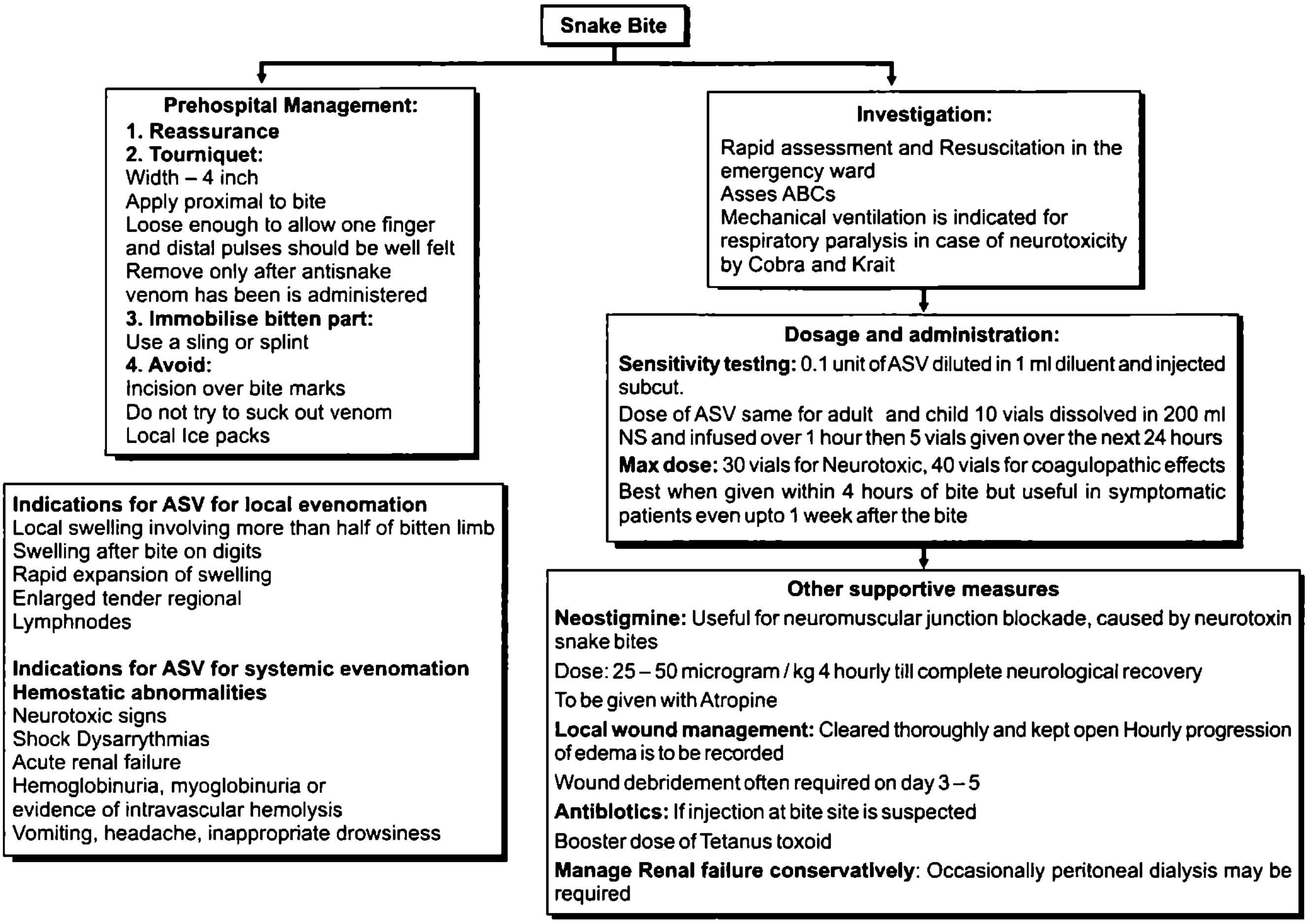
Flow chart 79.7 : Snake bite



Snake Bite

Prehospital Management:

1. Reassurance

2. Tourniquet:
Width – 4 inch
Apply proximal to bite
Loose enough to allow one finger and distal pulses should be well felt
Remove only after antisnake venom has been is administered

3. Immobilise bitten part:
Use a sling or splint

4. Avoid:
Incision over bite marks
Do not try to suck out venom
Local Ice packs

Indications for ASV for local evenomation
Local swelling involving more than half of bitten limb
Swelling after bite on digits
Rapid expansion of swelling
Enlarged tender regional Lymphnodes

Indications for ASV for systemic evenomation
Hemostatic abnormalities
Neurotoxic signs
Shock Dysarrythmias
Acute renal failure
Hemoglobinuria, myoglobinuria or evidence of intravascular hemolysis
Vomiting, headache, inappropriate drowsiness

Investigation:
Rapid assessment and Resuscitation in the emergency ward
Asses ABCs
Mechanical ventilation is indicated for respiratory paralysis in case of neurotoxicity by Cobra and Krait

Dosage and administration:

Sensitivity testing: 0.1 unit of ASV diluted in 1 ml diluent and injected subcut.

Dose of ASV same for adult and child 10 vials dissolved in 200 ml NS and infused over 1 hour then 5 vials given over the next 24 hours

Max dose: 30 vials for Neurotoxic, 40 vials for coagulopathic effects

Best when given within 4 hours of bite but useful in symptomatic patients even upto 1 week after the bite

Other supportive measures

Neostigmine: Useful for neuromuscular junction blockade, caused by neurotoxin snake bites

Dose: 25 – 50 microgram / kg 4 hourly till complete neurological recovery

To be given with Atropine

Local wound management: Cleared thoroughly and kept open Hourly progression of edema is to be recorded

Wound debridement often required on day 3 – 5

Antibiotics: If injection at bite site is suspected

Booster dose of Tetanus toxoid

Manage Renal failure conservatively: Occasionally peritoneal dialysis may be required

SCORPION STING

Scorpion bites are more common in the rural areas. In India 99 species of Scorpion are found, of these only two Mesobuthus tamulus (Indian red scorpion) and Palamneus Gravimanus (Indian black scorpion or "Ingali") are of medical importance. Mesobuthus tamulus smaller in size, is the most lethal of all scorpion species and is found in Maharashtra, Karnataka, Andhra Pradesh, Tamil Nadu, Gujarat and Pondicherry.[2] Scorpions prefer warm and dry regions, and are commonly found in underground burrows, crevices in dwellings, under debris and logs of wood, banana, sugarcane and coconut plantations and paddy husks. They are usually nocturnal predators and sting when disturbed in their hideouts. Clinical effect of Scorpion sting depends on factors like age of the victim (more in younger), order of sting (first or initial sting more severe), time lapse between sting and administration of vasodilators (the most important factor), use of drugs like atropine, steroids (increases mortality) and species of Scorpion (Mesobuthus tamulus causing severe cardiac manifestations).

Pathophysiology

Scorpion venom acts at the presynaptic nerve terminals by activating the sodium channel. It also blocks the calcium activated potassium channels, consequently there is excessive firing of the neurons resulting in an autonomic storm where both the sympathetic and parasympathetic systems are activated the scorpion toxin predominantly induces an alpha-receptor stimulatory effect resulting in pulmonary edema, respiratory distress, myocardial dysfunction, tachycardia, arrythmias, shock, hypertension and excessive sweating. Increased angiotensin I levels which gets converted to angiotensin II leads to increased sympathetic outflow. Metabolic effects mediated by alpha receptors stimulation are suppression of insulin secretion, hyperglycemia, hyperkalemia, free fatty acid accumulation and elevation of free radicals (responsible for myocardial damage). Direct toxic effect on neurons causes seizures and encephalopathy in few cases. Other manifestations are DIC, pancreatitis, hepatic necrosis and intravascular hemolysis leading to acute renal failure. "Autonomic storm" — cholinergic storm is initial and short lived while adrenergic storm is subsequent and more prolonged.

Clinical Features

Symptoms of Scorpion sting start within seconds to minutes and progress to reach maximum severity in five hours and usually subside within one to two days.[4] Hypertension usually occurs between three to five hours of envenomation and pulmonary edema between half an hour and 48 hours.

Local Pain

This clinical feature has inverse relationship with further progression of symptomatology. In those patients who have severe local pain, no further systemic manifestations (like autonomic storm, pulmonary edema etc) occur while those patients who have various systemic manifestations experience little or no local pain in the beginning. It is due to serotonin in Scorpion venom. Presence of local pain in the beginning and appearance of local pain after treatment which was absent in the beginning, both are good prognostic indicators. The former indicates nonpoisonous or nonbuthus sting and later indicates recovery from envenomation.

Cholinergic Storm: Patient initially shows signs and symptoms due to excessive acetylcholine production like vomiting, salivation, sweating (so conspicuous to call it skin diarrhea), bradycardia, priapism in males, increased bronchial secretions (bronchorrhoea) and constricted pupils. Hypotension due to volume loss can be seen.

Adrenergic Storm: In the inotropic phase there is tachycardia, hypertension, cold extremities and arrythmias. In the hypokinetic phase, hypertensive stress on myocardium, direct myocardial toxicity and catecholamine induced coronary spasm contributes to myoçardial dysfunction and leads to left ventricular failure causing important clinical feature of scorpion envenomation, i.e. cardiogenic pulmonary edema. Tachypnoea and intractable cough can be early indicators of developing pulmonary edema. The children with pulmonary edema have cold, clammy and pale skin, tachycardia, respiratory distress and sometimes pink frothy sputum. Left ventricular dysfunction also manifests with tachycardia and hypotension. Presence of pulmonary edema dose not always mean poor prognosis.

Neurological: Focal neurological deficits (aphasia, hemiplegia), intracranial bleed, seizures and altered sensorium are seen less commonly. When present they herald poor prognosis.

Terminal events: DIC and respiratory failure are usually terminal events.

Investigations

Investigations help in diagnosis and management of complications. Blood is sent for blood sugar levels, urea creatinine and liver enzymes. Hyperglycemia and hyperkalemia are often present. X-ray chest is obtained to look for evidence of pulmonary edema. ECG often reveals tall tented T waves, myocardial infarction pattern, prolonged QTc, left anterior hemiblock and low voltage are various changes seen. Echocardiography: LV dilation and LV systolic dysfunction are seen.

Management (Flow chart 79.8)

Pain Relief

Local pain may be managed with ice compression or paracetamol. When pain is severe, local lignocaine or dehydroemetine may be used.[5] Severe local pain at the site of sting is unlikely to progress to systemic manifestations.

Fluid Therapy

Early cholinergic storm may lead to profuse vomitings and diaphoresis can cause massive fluid loss and hypotension. If rapid cardio pulmonary assessment reveals dehydration or shock parenteral fluids are administered rapidly. Fluid must be administered carefully in children with LV dysfunction and pulmonary edema, preferably with CVP monitoring.

Scorpion Antivenom

It has not been found to be useful.

Prazosin

It is an antidote of Scorpion venom and should be used at the earliest. It is a postsynaptic, competitive, alpha-1 adrenergic receptor antagonist. It reverses both inotropic and hypokinetic phases as well as metabolic effects of depressed insulin secretions.[6] It is indicated at the earliest to patients with evidence of autonomic storm like vomitings, sweating, cold extremities etc. It is available as 1 mg tablet, sustained release forms of prazosin should not be used. Prazosin can be given orally or by nasogastric tube. First dose phenomenon (hypotension) can be prevented by plenty of oral fluids, not allowing child to sit or stand and monitoring of blood pressure – every 30 minutes for first 3 to 5 hours. Prazosin should be given irrespective of blood pressure in presence of good hydration. Prazosin is given in the dose of 30 microgram/kg/dose, repeated 3 to 4 hourly to maximum of four doses. Appearance of wide pulse pressure is an early clinical indicator of reduction of preload and afterload. Oral prazocin is cheap, fast acting, free from anaphylaxis, highly effective and easily available. It has decreased the mortality of scorpion envenomation from 30 percent to less than 1 percent.[7]

Management of Complications

Shock is managed with boluses of isotonic fluids. Since scorpion sting is commonly associated with myocardial dysfunction, initial fluid boluses should be started in smaller amounts (10ml/kg) upto 30-40 ml/kg. If shock does not improve consider initiating inotrope infusions. If there is deterioration (pulmonary edema or cardiogenic shock) then early intubation and ventilation is preferred to provide PEEP for pulmonary edema. Mild pulmonary edema can be managed with non-invasive positive pressure ventilation.

Vasodilators, such as sodium nitroprusside (0.5–4 mcg/kg/min) or nitroglycerine (5mcg/kg/min) infusions may be used in presence of cold shock. CVP monitoring helps adjust fluid therapy in the presence of myocardial dysfunction.

Signs of recovery: During recovery phase the general condition improves, extremities become warm and pulse volume increases. Sometimes hypotension can be seen during recovery which is attributed to exhausted catecholamine stores of body which are yet to be replenished in natural course (and does not need inotrope support). During recovery dilated veins are seen on extremities and paraesthesias disappear. Appearance of local pain, which was absent in the beginning heralds recovery.

Harmful Therapies to be Avoided

Atropine is given for symptomatic relief from clinical effects of cholinergic storm. It increases morbidity and mortality. Steroids potentiates the toxic effects of excess catecholamine on myocardium. Morphine can worsen cardiac arrythmias. Lytic Cocktail potentiates the effects of Scorpion venom, interfere with respiratory reflexes and prolongs hypotension. Nifedipine causes reflex tachycardia and has negative inotropic effect.

Captopril aggravates hyperkalemia.

Prognosis

1. Pain and age greater then 6 years are good prognostic signs.
2. Early use of Prazosin is associated with faster recovery.
3. Delay in starting Prazosin therapy, pulmonary edema, arrythmias, encephalopathy and age less then 6 years indicate a poor prognosis.

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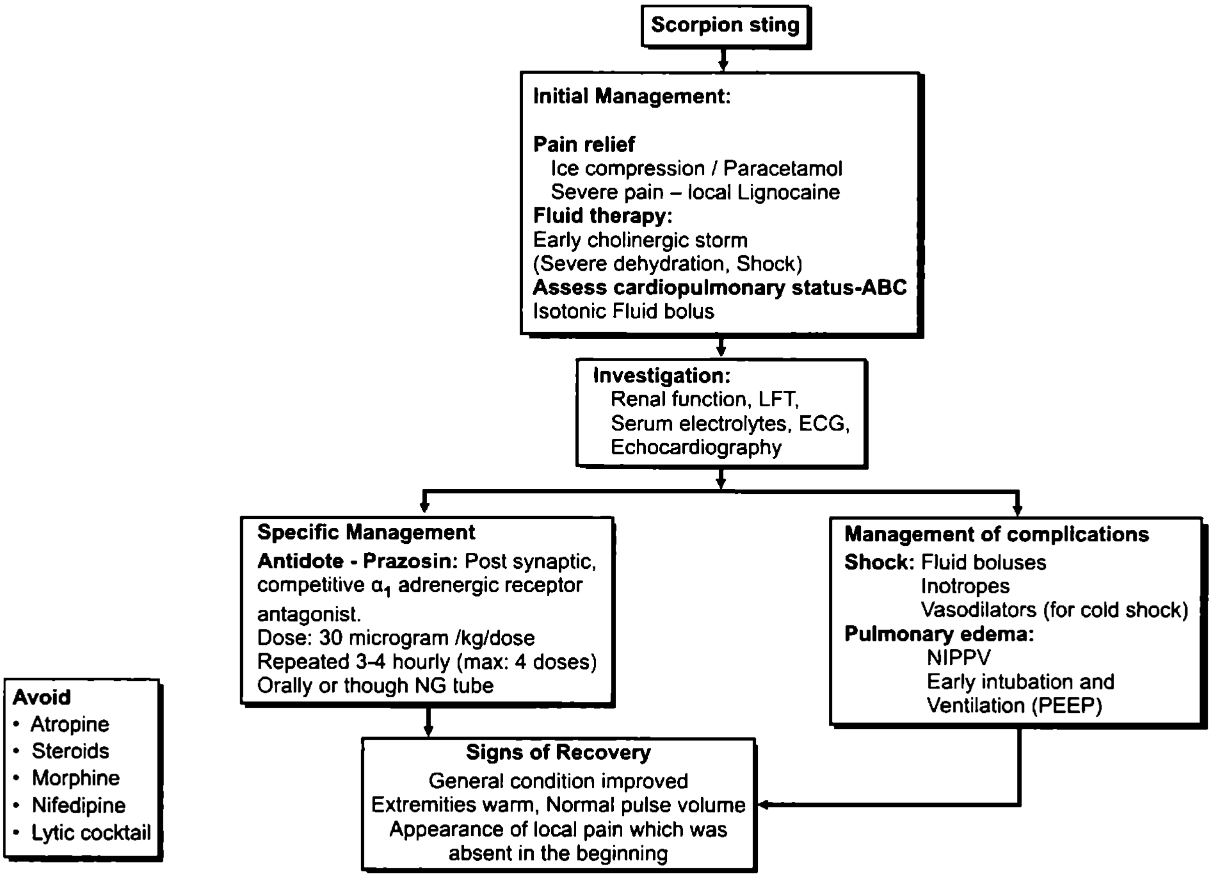
Flow chart 79.8 : Scorpion sting


Scorpion sting
Initial Management:
Pain relief
Ice compression / Paracetamol
Severe pain – local Lignocaine
Fluid therapy:
Early cholinergic storm
(Severe dehydration, Shock)
Assess cardiopulmonary status-ABC
Isotonic Fluid bolus
Investigation:
Renal function, LFT,
Serum electrolytes, ECG,
Echocardiography
Specific Management
Antidote - Prazosin: Post synaptic, competitive α1 adrenergic receptor antagonist.
Dose: 30 microgram /kg/dose
Repeated 3-4 hourly (max: 4 doses)
Orally or though NG tube
Management of complications
Shock: Fluid boluses
Inotropes
Vasodilators (for cold shock)
Pulmonary edema:
NIPPV
Early intubation and
Ventilation (PEEP)
Avoid
• Atropine
• Steroids
• Morphine
• Nifedipine
• Lytic cocktail
Signs of Recovery
General condition improved
Extremities warm, Normal pulse volume
Appearance of local pain which was absent in the beginning

CHAPTER 80

Methemoglobinemia

Sunil Gomber

Methemoglobin is an oxidized form of hemoglobin that is incapable of carrying oxygen.

This chapter addresses the issue of detection and clinical management of a child with methemoglobinemia in the pediatric intensive care unit (PICU).

Methemoglobin may be formed by a variety of oxidizing agents, including nitrate-containing well water as well as many medications, dyes, and industrial chemicals (Table 80.1). Methemoglobinemia could also be hereditary in nature.

The hereditary Methemoglobinemias are either due to the presence of one of the M-hemoglobins or due to the deficiency of cytochrome b5 reductase enzyme. These inherited disorders are clinically mild while the induction of methemoglobinemia by drugs or toxins can be life threatening.

Clinical Pharmacology and Toxicology

Oxidation of the heme iron from its normal ferrous (2+) state to the ferric (3+) state occurs regularly in the body owing to oxidants in ingested drugs, foods, and chemicals. *Most persons have a normal methemoglobin level of 1 to 2 percent.*

Table 80.1: Some causes of methemoglobinemia

- Local anesthetics
  - Benzocaine
  - Lidocaine
  - Antimicrobials
  - Chloroquine
  - Dapsone
  - Primaquine
  - Sulfonamides
  - Analgesics
  - Phenazopyridine
  - Phenacetin
- Nitrites and Nitrates
  - Amyl nitrite
  - Butyl nitrite
  - Isobutyl nitrite
  - Sodium nitrite
  - Miscellaneous
  - Aminophenol
  - Aniline dyes
  - Bromates
  - Chlorates
  - Metoclopramide
  - Nitrobenzene
  - Nitrogen oxides
  - Nitroglycerin

Physiologic mechanisms that normally prevent this level from rising incluse antioxidants such as Vitamin C and glutathione, and enzymes (NADH methemoglobin reductase and NADPH methemoglobin reductase) that reduce the ferric iron back to its usual oxidation state. Congenital disorders that result in elevated methemoglobin levels include hereditary NADH methemoglobin reductase deficiency and hemoglobin M disorder (hemoglobin M is an abnormal hemoglobin that is more susceptible to oxidation).

Methemoglobin is incapable of carrying oxygen, and its presence produces a functional anemia.

It may also interefere with oxygen delivery at the tissues by causing a leftward shift in the oxygen-hemoglobin dissociation curve.

Hereditary Methemoglobinemia

Cytochrome β5 Reductase Deficiency

This condition is inherited in an autosomal recessive pattern. The enxyme is a flavoprotein having properties similar to those of liver cytochrome β5 reductase. The soluble erythrocyte enzyme is formed by cleavage of a hydrophobic tail from the microsomal enzyme.

Four types of enzymopenic hereditary methemoglobinemia have been identified.

In type I, the most frequent of these rare disorders, a deficiency of cytochrome b5 reductase is limited to erythrocytes, and cyanosis is the only consequence.

Type II is a severe progressive disorder that accounts for approximately 10 percent of patients with hereditary methemoglobinemia. In this disorder the deficiency of cytochrome β5 reductase is generalized to all tissues. Affected individuals present with methemoglobinemia and severe encephalopathy, appearing before one year of age, and with mental retardation, microcephaly, strabismus, opisthotonos and generalized hypertonia.

In type III disease, the enzyme deficiency is demonstrable in erythrocytes, platelets, lymphocytes and granulocytes. Clinically cyanosis is the only manifestation.

Type IV disease results from a deficiency of erythrocytes cytochrome β5 and is associated with chronic cyanosis.

Untreated individuals usually have 15 to 30 percent methemoglobinemia. Levels are higher in older population of red cells because the activity of abnormal enzyme declines markedly with red cell age.

M-Hemoglobins[1-3]

Five Hb variants have abnormal absorbance spectrum, owing to the oxidation of hem iron in the affected subunit. They involve amino acid substitution of residues responsible for the binding of hem iron to the globin. These so called M-Hb results in a rare form of congenital HbM familial cyanosis. Individuals with alpha chain variants (HbM Boston and HbM Iwate) are cyanotic at birth, while cyanosis does not appear in those with beta chain variants (HbM Saskatoom, HbM Hyde Park, HbM Milwaukee) until about 4-6 months of age, when fetal Hb has been replaced by adult Hb. Except for cyanosis, patients are asymptomatic.

Acquired Methemoglobinemia

This disorder is generally due to exposure to certain drugs or toxins. Some drugs such as nitrite and chlorate oxidize hem iron directly. Others such as sulfa drugs and aniline dyes must undergo biochemical transformation before they cause methemoglibinemia (Table 80.1).

As might be expected, individuals heterozygous for methemolgobin reductase are much more likely than normal individuals to develop apparent methemoglobinemia after exposure to an oxidant stress. Thus the extent of methemoglobinemia depends not only on the dose of toxic agent but also on the susceptibility of the exposed individuals.

The newborn infant is usually susceptible on exposure to toxic agents as there is increased sensitivity of foetal erythrocytes to oxidizing agents causing formation of foetal methemoglobin.[5] This has been shown to be function of gamma chain of HbF. Moreover, there is a transient physiologic deficiency of cytochrome β5 reductase activity in neonates (approx. 60% of the normal adult value). Even reduction in activity is found in premature neonates.

Clinical Features

The clinical features of methemoglobinemia are determined not only by the concentration of methemoglobin, but also by its rate of formation. Additionally, the compounds producing methemoglobin may also have their own toxic effects. The important feature of methemoglobinemia includes nausea, vomiting, headache, giddiness, drowsiness, coma and respiratory depression. Table 80.2 lists the important features depending upon the concentration of methemoglobin. It should be emphasized that patients with underlying cardiopulmonary diseases will have symptoms with lesser degree of methemoglobinemia as compared to healthy individuals.

Diagnosis

Methemoglobinemia should be considered in any cyanotic patient with no evidence of heart or lung disease.

Red Brown Screening Test

Blood with high levels of methemoglobin is chocolate coloured when placed on filter paper as compared to normal blood. The color does not revert to pink with oxygen but

Table 80.2: Clinical features of methemoglobinemia

Methemoglobin concentration	*Clinical features*
0-3%	Normal
3-15%	Usually no features
15-20%	A symptomatic but cyanosis present
20-25%	Dyspnea, headache, fatigue, syncope, weakness, dizziness.
50-70%	Tachypnea, metabolic acidosis, seizures, arrythmias, CNS depression, coma.
>70%	Coma, Death.

does return to normal when exposed to 10 percent potassium cyanide.

Arterial Oxygen Tension

Arterial oxygen tension is relatively unaltered in methemoglobinemia despite presence of cyanosis. This is because partial pressure of oxygen in blood is a measure of adequacy of pulmonary function and is not affected by levels of normal Hb4.

Arterial O_2 Saturation

If all types of hemoglobins are measured by an oximeter, the *measured arterial oxygen saturation is reduced.*

Only a few oximeters can measure oxygen saturation as a ratio of oxy-Hb to total Hb (including all types of Hb). This is called fractional O_2 saturation.

However, most oximeters measure functional O_2 saturation i.e. the ratio of oxy-Hb to total Hb i.e. bound to O_2 or is available for binding O_2 (i.e. sum of oxy-Hb and deoxy-Hb).

Carboxy-Hb, met-Hb and sulph-Hb are therefore, not measured. In such cases, the measured saturation may not be significantly different from the calculated saturation.

Spectrophotometry

Methemoglobin is identified by its absorption at a frequency of 630 nm by spectrophotometry. Individuals with hereditary methemoglobinemia will have levels lower than patients symptomatic from acquired causes.

Patients who have ingested an oxidant drug may have an additional Hb derivative called sulph Hb in which the protoporphyrin has been chemically modified.

Sulphemoglobinemia tends to cause cyanosis even more readily. Unlike metHb, the absorbance of sulphHb at 620-630 nm is not decreased by the addition of cyanide. The M-Hb have characteristics spectral abnormalities which differ from those obtained when normal HbA is partially oxidized. Furthermore these Hb variants can be detected by Hb electrophoresis.

Management

Hereditary Methemoglobinemia

In individuals with metHb reductase deficiency, the oral administration of methlene blue (3-5 mg/kg) or ascorbic acid (200-500 mg/day) will result in a marked reduction in the level of metHb.

The purpose of treatment is primarily cosmetic. Treatment is neither necessary nor possible in individuals having HbM.

Acquired Methemoglobinemia

For most patients with mild methemoglobinemia, no treatment is required other than the withdrawal of the offending agent as reduction of metHb will occur within 24-72 hours by means of NADH-MetHb reductase. *If the symptoms are pronounced or metHb levels are more than 30 percent, treatment to hasten the conversion of metHb to active Hb is required.*

This should follow the usual methods of decontamination and supportive management in the PICU.

- The toxin, if recently ingested, should be removed by gastrointestinal decontamination followed by administration of activated charcoal and cathartics. Most of oxidizing agents are metabolized rapidly, making diuresis ineffective.
- *Administer methylene blue intravenously (I.V) in a dose of 1-2 mg/kg of body wt in a 1 percent solution slowly over five minutes.*

Improvement is noted within one hour of its administration. If significant improvement does not occur within an hour, administer a second dose of methylene blue should be given.

Mechanism of Action of Methylene Blue

When methylene blue is administered, the NADPH-metHb reductase complex reduces it to leuco-methylene blue which in turn reduces metHb to a normal Hb state rapidly. Since NADPH is generated in the HMP (Hexose monophosphate) shunt pathway in which G6PD (glucose 6 phosphate dehydrogenase) is one of the enzymes, *methylene blue is ineffective if either metHb reductase or G6PD is deficient in an individual.*

If treatment with methylene blue fails, one should consider the possibility of continuous exposure. Therefore one must resume decontamination of gut and skin. It should also be understood that some of the agents (e.g. acetanilide, phenacetin, nitrites, trinitrotoluene and others) besides producing methemoglobinemia also produce sulphemo-globinemia and therefore may lead to an apparent non-responsiveness to cyanosis.

Therefore, measurement of metHb is mandatory in such situations.

Methylene blue causes a bluish discoloration of the skin and urine creating a cyanotic appearance and making clinical assessment difficult. In higher doses (> 5 mg/kg), methylene blue itself produces methemoglobinemia and hemolysis.

Vitamin C has probably little role in managing methemoglobinemia as the rate at which it reduces metHb is considerably slower than that of the normal intrinsic mechanism. *However, as methylene blue is not easily available in India, vitamin C may be tried in a dose of 500-1000 mgIV.*

If there is no response, an *exchange transfusion, hemodialysis or hyperbaric oxygen may be beneficial especially when metHb concentration is 70 percent or more.*

These patients will show evidence of metabolic acidosis and hypotension, will require ventilatory support with continuous arterial blood pressure monitoring as well as central venous pressure monitoring, with inotropic support until level of methemoglobin drops with improving metabolic acidosis. This condition is associated with considerably high mortality.

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Section Nine

Infections and Infection Control

CHAPTER

81

Antibiotic Therapy in the Pediatric Intensive Care Unit

Praveen Khilnani

Many antibiotics are commonly used in the pediatric intensive care unit (PICU) simultaneously, on an empirical basis. Purpose of this chapter is to put this therapy in proper perspective and discuss newer anti-biotics and their rational use. The diagnosis and therapy of infections in PICU setting remains a major function of the pediatric critical care specialist (pediatric intensivist). PICU infections are often severe and seen either as a cause of severe illness requiring admission to the PICU, such as septic shock, ARDS (acute respiratory distress syndrome) or as a complication of other severe illnesses requiring admission to PICU such as major multiple trauma, neuromuscular disorders requiring prolonged ventilation (nosocomial infections), immunodeficiency states, postoperative transplant patients and postoperative surgical patients.

Infections and Empirical Therapy (Table 81.1)

Infections may have dramatic presentation with high temperatures, leukocytosis with left shift, hypotension, disseminated intravascular coagulopathy, renal insufficiency, and respiratory failure. On the other hand, patients admitted to PICU for presumed shock, respiratory insufficiency, or coma may ultimately not have infection as an underlying diagnosis despite the presence of classic signs and symptoms.

As a general principle, while empirical therapy should be promptly started based on clinical setting, main goal should be to identify the infecting pathogen by staining techniques (such as gram stain) and through isolation of the pathogen by culture and later modifying the antibiotic therapy, according to appropriate sensitivity patterns. This may not always apply to pretreated or partially treated infections, but nevertheless cultures must be obtained wherever feasible. Usefulness of gram stain and culture specimen is directly related to care with which the specimen is obtained. Compulsive care must be used to minimize contamination during specimen collection, as much as possible.

Criteria for Selection of Antibiotics

History and Clinical Setting

Several aspects of patient's history and the clinical setting must be considered.

1. *Is the infection community acquired or hospital acquired?*
   Community acquired infections are usually easy to treat with standard narrow spectrum less expensive antibiotics. Hospital acquired infections are usually caused by pathogens with complex antimicrobial resistance patterns requiring potentially more toxic and expensive antimicrobial agents.
2. *What is the patients underlying illness?* For example, leukemia, burns and cystic fibrosis (*Pseudomonas aeruginosa*) diabetes (anaerobes and *Staphylococcus Aureus*), HIV (Human immunodeficiency virus) and immunodeficiencies (Pneumocystis, Candida, Herpes, Cytomegalovirus and Mycobacterial infections).
3. *What is the suspected site of the primary infection?* For example, urinary tract and biliary tree (enteric aerobic gram negative bacilli), endocardium (aerobic gram positive cocci (*S. aureus, S. viridans*),

Table 81.1: Choice of empirical antibiotic in patients with septic shock with respect to clinical settings

Clinical setting	*Usual pathogens*	*Preferred therapy*	*Alternate therapy*
Unknown source from the community	Salmonella typhi/ paratyphi *S. pneumoniae* *H. influenzae* *Enterobacter* *B. fragilis* *E. fecalis* Think of malaria and dengue	Ceftriaxone plus Metronidazole or Piperacillin/ Tazobactam or Meropenem or Imipenem	Quinolone (Ciprofloxacin/ Levofloxacin) plus either Metroindazole or Clindamycin
Lung source	*S. pneumoniae* *H. influenzae* *Staphylococcus aureus* *M. pneumoniae*	Ceftriaxone/ cefotaxime/amoxicillin calvulanic acid and azithromycin/ clarithromycin	Substitute new fluoroquinolone (levofloxacin/ gatifloxacillin) for macrolide
IV line sepsis	*S. epidermidis* *S. aureus* (Methicillin sensitive *Staph aureus*) Klebsiella Enterobacter Serratia	Vancomycin plus Meropenem or Imipenem or Cefepime or Piperacillin/ Tazobactem	May substitute linezolid for vancomycin Add antifungals if fungus suspected
Urosepsis	Entero-bacteriaceae	Ceftriaxone or Cafotaxime or Quinolone	Aztreonam or Ampicillin + Amikacin
Meningitis	*S. pneumoniae* *H. influenzae* *N. meningitidis*	Ceftriaxone or Cefotaxime	Add vancomycin if drug resistant pneumococci suspected
Intra-abdominal source	Enterobacter *B. fragilis* enterococci	Ceftriaxone plus Metronidazole or Piperacillin/ tazobactam or Meropenem or Imipenem	Quinolone (Ciprofloxacin/ Levofloxacin) plus either Metronidazole or Clindamycin

or meninges (*S. pneumoniae, N. meningitidis* and *H. influenzae*).

Pharmacology

A reasonable understanding of *pharmacology* including the knowledge of whether the antibiotic agent is bacteriostatic or bactericidal, its antimicrobial spectrum, pharmacokinetics, toxicities and dosing intervals, is required.

Bactericidal drugs (drugs that kill bacteria) are needed in conditions such as meningitis due to decreased complement level and lack of surface phagocytosis, and in endocarditis, due to vegetations being impermeable to white cells or in neutropenic patients. *Bacteriostatic drugs (drugs that prevent multiplication of bacteria)* are usually adequate if host defences are intact.

The intensivist also needs to keep well informed regarding hospital *antibiogram* (responsibility of the microbiology department) that outlines susceptibility of common hospital specific pathogens as this may vary from hospital to hospital.

Pharmacokinetics

A good knowledge of pharmacokinetics is important. For example, biliary or urinary tract concentration, meningeal penetration needs to be kept in mind while treating the respective infections. A good working knowledge of toxicity profile of various antimicrobials and modification of dosage regimen in liver failure or renal insufficiency is also equally important.

Strategy in Case of Clinical Deterioration

During first 48 to 72 hours of empirical antibiotic therapy, the patient must be watched for signs of clinical deterioration or improvement.

If patient's condition deteriorates, following possi-bilities should be considered.

1. Undrained or undebrided focus of infection.
2. Too narrow spectrum of antimicrobial coverage.
3. Inadequate penetration of drug to the focus of infection.
4. Sub-therapeutic dose/interval for the severity of infection or size of the patient.
5. In frank septic shock once inflammatory cascade, cytokine response has set in, this may, despite ade-quate antibiotic therapy, still lead to unfavorable outcome.

Nevertheless, early and appropriate empirical antibiotic therapy in all suspected infections is strongly recommended in intensive care setting.

Empirical Initial Antimicrobial Therapy in the PICU

Following is a broad guideline for initial antibiotic therapy, individual clinical situation may vary from patient to patient warranting a change in antimicrobial therapy.

Sepsis Syndrome

First Line therapy

Third generation cephalosporin and aminoglycosides like Cefotaxime/Ceftriaxone and Amikacin may be used.

Alternative therapy Quinolones (Ofloxacin, Ciprofloxacin), or Impenem.

Acute Respiratory Distress Syndrome

Antibiotic therapy depends on underlying cause such as septic shock (gram negative/gram positive sepsis), or primary pulmonary cause such as aspiration pneumonia.

Pneumonia

Community acquired pneumonias tend to be due to Pneumococcus, Staphylococcus, or atypical microbes such as Mycoplasma infections.

S. Pneumoniae is treated by using, penicillin group of antibiotics, or first generation cephalosporin, or a second generation cephalosporin such as cefuroxime plus a macrolide (erythromycin, clarithromycin or azithromycin) to cover for Mycoplasma pneumonia.

Staphylococcal pneumonia is best treated by augmentin (amoxicillin with clavulanic acid) or cloxacillin plus gentamicin for synergistic activity.

A reasonable cost-effective combination would be Ampicillin and cloxacillin. Aspiration pneumonia could be effectively treated by ampicillin, amikacin and metronidazole. Clindamycin has good anerobic and staphylococcal coverage.

Hospital acquired Staphylococcal pneumonias are usually resistant to anti-Staphylococcal pennicillins and therefore are best treated with vancomycin.

For *hospital acquired pneumonias due to Pseudomonas* use of ceftazidime in combination with quinolones (ofloxacin/ciprofloxacin/levofloxacin) or an aminoglycoside such as amikacin may be appropriate.

Pneumonia in Immunocompromized host should be treated as hospital acquired pneumonia treated with broad spectrum antibiotics as mentioned above empirically until culture results become available. One should consider adding acyclovir/antifungal therapy depending on clinical setting.

Abdominal Sepsis

Sepsis secondary to necrotising enterocolitis, peritonitis due to gut perforation warrants both gram negative and anaerobic coverage. Augmentin or ceftriaxone/cefotaxime in combination with metronidazole is a reasonable antibiotic choice. Alternatively ampicillin, gentamycin and clindamycin (or metronidazole) is a good broad spectrum combination.

In patients with nephrotic syndrome pneumococcal peritiniotis can be adequately covered by augmentin. In cases of renal or urinary tract infections, such as pyelonephritis—a combination of aminoglycoside, such as amikacin plus cefotaxime may be used. In patients with enteric fever or colitis due to E. coli, Klebsiella, or Shigella cefotaxime/ quinolone and metronidazole combination may be indicated.

Central Nervous System (CNS) Infections

Meningoencephalitis

- Therapy is based on suspected organisms:
  - *Herpes simplex:* Acyclovir
  - *Niesseria meningitidis, H Influenzae, Strep pneumoniae:* Ceftriaxone
  - *E. coli meningitis:* Cefotaxime and gentamicin
  - *Brain abscess:* Ceftriaxone plus Augmentin
  - *Mastoid abscess:* Ceftazidime

Ventriculoperitoneal Shunt Infection

Vancomycin is indicated to cover for *S. epidermidis* and *S. aureus* infection. In addition *ceftriaxone* is needed to cover for gram negative bacteria. Shunt may need to be removed for resistant pseudomonas infections.

Endocarditis

Strep viridans is a common organism responsive to a combination of pencillin and gentamicin/amikacin therapy.

Staph. aureus endocarditis is covered adequately by Cloxacillin and Gentamicin/Amikacin.

Methicillin Resistant Staph. Aureus (MRSA) Vancomycin (Hospital acquired infections) is drug of choice.

Enterococcal endocarditis (Strep Fecalis) is treated with vancomycin and gentamicin.

Invasive Lines and Catheters

Urinary catheter related infections are treated with aminoglycosides until cultures are available. Catheter should be changed or removed.

Central line related infections are empirically treated with Vancomycin and an aminoglycoside to cover for *Staph epidermidis* and gram negative bacteria.

In resistant infections line and catheters should be removed. Peripheral intravenous line may be used for 48 hours or alternatively another central line should be placed at a different site if intravenous access is difficult. Guidewire change of central line is not routinely recommended for prevention of central line infection.

Postoperative Empirical Antibiotics

These are not indicated routinely in postoperative surgical ICU. Individual clinical situation will warrant antibiotic coverage in perioperative period depending on underlying illness.

Neurosurgical

Ventricuio peritoneal shunt related coverage: vancomycin and ceftriaxone.

Neck surgery: Augmentin

Heart surgery: Ceftriaxone and vancomycin

Chest: Augmentin and ceftazidine, specially in patients with cystic fibrosis where *Pseudomonas aeruginosa* and *Pseudomonas cepacia* lower respiratory tract infections are a common occurrence. Tobramycin by nebulizer may be indicated in such cases.

Empyema Due to suspected *Staph aureus: Vancomycin/ Cloxacillin.* In cases of empyema due to gram negative organisms cefotaxime/gentamicin. In case of resistant organisms imepenem may be required.

Abdominal surgery: Cefotaxime plus metronidazole

Orthopedics surgery: Ceftriaxone

Septic arthritis or Osteomyelitis surgery: Vancomycin

Fungal Infections

Fungal infections should be strongly suspected in patients with fever spikes and leukocytosis who have been on broad spectrum antibiotics for longer than two weeks, as well as in immunocompromized children, children with malignancies, HIV and nephrotic syndrome.

Deep seated or *blood infections require*
Amphotericin B
Caution: Renal insufficiency and hypokalemia

Urine culture may be positive for Candida Albicans necessitating Intravenous fluconazole in combination with amphotericin bladder irrigation. Fluconazole, Intraconazole, Caspofungin, anidulafungin are some of the newer antifungal agents.

Empirical Antibiotic Therapy in Renal Failure

Dosages of following antibiotics need to be modified:

Aminoglycosides, Vancomycin, Cephalosporins, Amphotericin. Liposomal amphotericin may be tried in hepatic and renal failure.

Following antibiotics are relatively safe:

- Quinolones
- Augmentin
- Ceftriaxone
- Cefoperazone.

Liver Failure

- Avoid cephalosporins in general.
- Cefoperazone has been used, relatively safe.
- Amoxicillin, imipenem, quinolones, and
- Aminoglycosides

Vancomycin use in pediatrics: Red book 2000 recommendations:

Indications of vancomycin:

1. Gram positive beta lactam resistant organisms
2. Gram positive infections with allergy to beta lactam antibiotics
3. Antibiotic associated colitis not responding to metronidazole
4. Endocarditis prophylaxis
5. Prosthetic surgical procedure prophylaxis.

Vancomycin should not be used in the following situations:

1. For routine surgical prophylaxis
2. Empirically if cultures negative for beta lactam resistant organisms
3. For prophylaxis for central lines
4. For selective gastrointestinal decontamination
5. For Eradication of MRSA colonization.

Alternative to Vancomycin: Teicoplanin

Teicoplanin has same antibacterial spectrum used in patients sensitive to vancomycin (Targocid) 10 mg/kg/dose intravenously 12 hourly.

Newer Antibiotics

Following is a brief mention of some of the newer antibiotics:

a. *Carbepenems:* Imepenem and, Artapenem and Doripenem
b. *Monobactems:* Aztreonam
c. *Newer Macrolides:* Clarithromycin and Azithromycin
d. *Quinolones:* Ciprofloxacin and Ofloxacin, Nor-floxacin, Enoxacin, Levofloxacin, Lomifloxacin, Sparfloxacin and Trovafloxacin
e. *Newer cephalosporins:* Fourth generation cephalosporins such as Cefipime, Cefradine, Cefonicid, Cefpodoxime, Ceftibuten and Cefdinir
f. Piperacillin and Tazobactams (Zosyn)/Ampicillin and Sulbactam (Unasyn, ticarcillin and clavulanic acid (Timentin).
g. Tigecyaline h. Oxazolidinones Linezolid

Carbepenems

Imepenem and Meropenem

These are indicated for resistant hospital acquired gram negative infections such as Acinetobacter, Enterobacter, Klebsiella, Proteus, Pseudomonas species as well as aerobic gram positive bacteria such as staph. These have good CSF penetration.

Imepenem (Primaxin) 40-60 mg/kg/day 4 doses IV. With *Meropenem (60-120 mg/kg/day three doses)* there is lesser incidence of seizures when compared to Imepenem.

Caution: These drugs do not cover Enterococcus, Chlamydia, Mycoplasma, Legionella and Listeria.

Monobactems such as Aztreonam are active against aerobic gram negative bacilli such as Pseudomonas, Serratia, Klebsiella and Enterobacter species.

Aztreonam is available as 500 mg vial, in doses of 90–120 mg/kg/day, 3 to 4 doses IM or IV.

Other relatively newer antibiotics are:

Newer Macrolides

Clarithromycin and Azithromycin (oral as well as intravenous preparations are available): Useful for community acquired gram positive infections including Mycoplasma Pneumonia.

Quinolones

Good broad spectrum gram positive and gram negative cover including enteric, and urinary tract infections.

Drugs include
Ciprofloxacin, Ofloxacin, Norfloxacin, Enoxacin, Levofloxacin, Lomifloxacin, Sparfloxacin and Trovafloxacin.

Caution Necrosis of developing cartilage arthropathy (Pefloxacin).

Ciprofloxacin has been found to be safe in children 20- 30 mg/kg/day given in two doses.

Alatrofloxacin, Trovofloxacin can cause acute liver failure.

Main indications include the following:

- UTI due to Pseudomonas
- Mycobacterial other multidrug resistant enteric/ gram negative bacterial infections
- Chronic suppurative otitis media
- Chronic osteomyelitis
- Cystic fibrosis exacerbation
- Oral therapy in immunocompromized host

Newer Cephalosporins

Fourth generation cephalosporins with excellent gram negative coverage are available.

- Cefipime IV or IM 100 to 150 mg/kg/day three doses.
- Cefradine 25 to 50 mg/kg/day two to four doses PO.
- 50 to 100 mg/kg/day IV in four doses.
- Cefonicid IV/IM 20 to 40 mg/kg single dose.
- Cephalosporins available in India are Cefpodoxime 10 mg/kg/day given in two doses, Ceftibuten PO, 9 mg/kg/day, one dose and Cefdinir (Cefdin).

Other antibiotics
Following are mainly used for gram negative resistant infections including pseudomonas infections.

Piperacillin and tazobactams (Zosyn) 240 mg/kg/ day, three doses (not approved for children)/ Ampicillin and Sulbactam (Unasyn) 200 to 400 mg/ kg/day, ticarcillin and clavulanic acid (Timentin) 100 to 300/kg/day, in four doses.

Other Newer Antibiotics Include

Streptogramins (Quinapristin-dalfopristin). These antibiotics are meant for treating gram positive infection, specially vancomycin resistant *Strep faecalis* (enterococcus), nosocomial pneumonia, central line related infections.

Everninomycin is used for gram positive nosocomial infections in intensive care units.

Linezolid is also a new antibiotic used for gram positive infections.

Telithromycin (a newer ketolide antibiotic) for respiratory infections.

CARBAPENEM

Meropenem

Meropenem is a synthetic bactericidal antibiotic belonging to 'Carbapenem' group of antibacterial agents with a broad spectrum of activity against gram-negative, gram-positive and anaerobic microorganisms. Meropenem has clinical and bacteriological efficacy in treatment of various serious infections in children and its use in Pediatrics has increased significantly specially in the intensive care units in the last few years.

Pharmacokinetics

Meropenem penetrates well into most body fluids and tissues including cerebrospinal fluid (penetration is better in inflammed meninges), achieving concentrations matching or exceeding those required to inhibit most susceptible bacteria. After a single intravenous dose of Meropenem, the highest mean concentrations of meropenem is found in tissues and fluids at 1 hour (0.5 to 1.5 hours) after the start of infusion. Meropenem is primarily excreted by the kidney with about half to three-fourths of dose excreted unchanged in the urine and a further one-fourth excreted as a microbiologically inactive open β-lactam metabolite. In children with normal renal function, the elimination half-life of intravenous Meropenem is approximately 1 hour. Approximately 70 percent of the intravenously administered dose is recovered as unchanged Meropenem in the urine over 12 hours, after which little further urinary excretion is detectable. Plasma protein binding of meropenem is approximately 2 percent. There is one metabolite which is microbiologically inactive. Meropenem is stable against hydrolysis by human renal dehydropeptidase (DHP-1) and Unlike Imipenem, concomitant administration of cilastatin (DHP inhibitor) is not required.

Microbiology

Meropenem is active against Gram-positive and Gram-negative bacteria, it's bactericidal activity results from the inhibition of cell wall synthesis. Meropenem readily penetrates the cell wall of most Gram-positive and Gram-negative bacteria to reach penicillin-binding-protein (PBP) targets. Its strongest affinities are toward PBPs 2, 3 and 4 of *Escherichia coli* and *Pseudomonas aeruginosa;* and PBPs 1, 2 and 4 of Staphylococcus aureus. Bactericidal concentrations (defined as a 3 log10 reduction in cell counts within 12 to 24 hours) are typically 1-2 times the bacteriostatic concentrations of meropenem, with the exception of Listeria monocytogenes, against which lethal activity is not observed. Meropenem has significant stability to hydrolysis by β-lactamases of most categories, both penicillinases and cephalosporinases produced by Gram-positive and Gram-negative bacteria. Meropenem should not be used to treat methicillin-resistant staphylococci (MRSA). In vitro tests show meropenem to act synergistically with aminoglycoside antibiotics against some isolates of Pseudomonas aeruginosa.

Meropenem is useful as presumptive therapy in the indicated condition (i.e., intra-abdominal infections) prior to the identification of the causative organisms because of its broad spectrum of bactericidal activity. Antimicrobial therapy should be adjusted, if appropriate, once the results of culture(s) and antimicrobial susceptibility testing are available.

Spectrum of Activity

Aerobic and Facultative Gram-positive Microorganisms

Meropenem is active against a large number of gram negative organisms including *Enterococcus faecalis* (excluding vancomycin-resistant isolates), *Staphylococcus aureus* (β-lactamase and non-β-lactamase producing, methicillin-susceptible isolates only), *Streptococcus agalactiae, Streptococcus pneumoniae* (penicillin-susceptible isolates only), *Streptococcus pyogenes,* Viridans group streptococci.

Aerobic and Facultative Gram-negative Microorganisms

Nearly all Gram-negative bacteria including those producing extended spectrum β-lactamases (ESBL) are susceptible to Meropenem including Escherichia coli, Haemophilus influenzae (β-lactamase and non-β-lactamase producing), *Klebsiella pneumoniae, Neisseria meningitides, Pseudomonas aeruginosa, Proteus mirabilis Acinetobacter species, Campylobacter jejuni, Citrobacter diversus oraxella catarrhalis, Citrobacter freundii, Morganella morganii,* Enterobacter cloacae, Proteus vulgaris, Salmonella species, Serratia marcescens, Shigella species, Yersinia enterocolitica.

According to a study 99 to 100 percent of isolates of Gram negative bacteria were susceptible to Meropenem, which was significantly better than imipenem, ciprofloxacin, piperacillin β- tazobactum, cetotaxime and ceftazidime. Gram-negative bacteria considered to be highly susceptible to meropenem included Hemophilus influenzae and Neisseria meningitis. Meropenem was more effective than imipenem against *P. aeroginosa.*

A recent multicentric surveillance study from India found Meropenem to be the most active amongst the ten antimicrobial agents tested against a total of 212 Gram-negative isolates of which 125 were extended spectrum β-lactamase (ESBL) producers. The order of susceptibility was meropenem (99% susceptible) > piperacillin/tazobactam (77%) > ciprofloxacin (43%) > aminoglycosides and other β-lactams (30-40%). Of all the srains tested only Acinetobacter spp. and *Pseudomonas putida* showed an intermediate susceptibility to Meropenem. *Escherichia coli* and Klebsiella had high levels of resistance against other drugs tested but were susceptible to Meropenem.

Anerobic Microorganisms

Bacteroides distasonis, Eubacterium lentum, Bacteroides ovatus, Fusobacterium species, Bacteroides uniformis, Prevotella bivia, Bacteroides ureolyticus Prevotella intermedia, Bacteroides vulgatus, Prevotella melaninogenica, Clostridium difficile, Clostridium perfringens, orphyromonas asaccharolytica.

Indications

Meropenem is used in treating pediatric meningitis and severe infections in intensive care settings. It has also been used to treat septicemia, febrile neutropenia, lower respiratory tract infections including those in cystic fibrosis, and urinary tract infections. Susceptibility of gram negative isolates (including ESBLS producers) to meropenem is superior to other new beta lactams such as Aztreonam, piperacillin + tazobactam and newer cephalosporins. Meropenem is indicated as single agent therapy for the treatment of the following infections when caused by susceptible isolates of the designated microorganisms:

Skin and Skin Structure Infections

Complicated skin and skin structure infections due to Staphylococcus aureus (β-lactamase and non-β-lactamase producing, methicillin susceptible isolates only), *Streptococcus pyogenes, Streptococcus agalactiae,* and viridans group streptococci, Enterococcus faecalis (excluding vancomycin-resistant isolates), *Pseudomonas aeruginosa, Escherichia coli, Proteus mirabilis, Bacteroides fragilis,* and *Peptostreptococcus* species.

Intra-abdominal Infections

Complicated appendicitis and peritonitis caused by viridans group streptococci, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacteroides fragilis, B. thetaiotaomicron,* and *Peptostreptococcus* species.

Bacterial Meningitis

Meropenem is recommended bacterial meningitis in children above 3 months of age, caused by Streptococcus pneumoniae, *Haemophilus influenzae* (β-lactamase and non-β-lactamase-producing isolates), *Neisseria meningitides, Klebsiella* and other enterobacteriaceae. The efficacy of meropenem as monotherapy in the treatment of meningitis caused by penicillin nonsusceptible isolates of *Streptococcus pneumoniae* has not been established. Meropenem has been found to be effective in eliminating concurrent bacteremia in association with bacterial meningitis. Appropriate cultures should usually be performed before initiating antimicrobial treatment in order to isolate and identify the organisms causing infection and determine their susceptibility to Meropenem.

Febrile Neutropenia

Meropenem is useful as an empirical monotherapy for infections in patients with febrile neutropenia in whom Gram-positive organisms such as staphylococci and streptococci account for 50 percent of infections in patients with neutropenia, while enterobacteriacae are also frequently encountered.

Use in Critically Ill Children

Meropenem is an effective and safe treatment for infants and children with serious infections (*e.g.*, urinary tract infections, pneumonia, sepsis, intra-abdominal infections, and skin and soft-tissue infections) including nosocomial infections. Meropenem monotherapy is as effective as imipenem/cilastatin in clinical and bacteriological responses. Meropenem monotherapy is significantly more effective than ceftazidime-based combination treatments inpatients with nosocomial lower respiratory tract infections (LRTIs).

Contraindications

Meropenem is contraindicated in patients with known hypersensitivity to any component of this product or to other drugs in the same class or in patients who have demonstrated anaphylactic reactions to β-lactams.

Dosage and Administration

For children from 3 months of age and older, the Meropenem IV dose is 10, 20 or 40 mg/kg every 8 hours (maximum dose is 2 g every 8 hours), depending on the type of infection (complicated skin and skin structure, intra-abdominal or meningitis). Pediatric patients weighing over 50 kg should be administered intravenous Meropenem at a dose of 500 mg every 8 hours for complicated skin and skin structure infections, 1 g every 8 hours for intra-abdominal infections and 2 g every 8 hours for meningitis.

Recommended meropenem IV Dosage Schedule for Pediatrics with Normal Renal Function:

Type of infection	Dose (mg/kg)	Up to maximum dose	Dosing interval
Complicated skin and skin structure	10	500 mg	Every 8 hours
Intra-abdominal	20	1 g	Every 8 hours
Meningitis	40	2 g	Every 8 hours

Meropenem should be given as intravenous infusion over approximately 15 to 30 minutes or as an intravenous bolus injection (5 to 20 mL) over approximately 3-5 minutes. For bolus injection, the drug should be reconstituted with sterile water and for IV infusion, it may be reconstituted with compatible intravenous fluids like glucose or saline solutions. Drug reconstituted with sterile water maintains its potency at room temperature (up to 25°C) up to 8 hours and under refrigeration (4°C) for 48 hours. The drug should be used with caution in patients with history of hypersensitivity reactions to β-lactam antibiotics.

Use in Renal Failure

In patients with renal failure (Creatinine clearance less than 50 mL/min) lower dosages should be used. The frequency should be reduced to 12 hourly in those having creatinine clearance between 26 and 50 mL/min. At creatinine clearance of 10-25 mL/min, one-half of the unit dose should be given 12 hourly whereas for values below 10 mL/min, one-half of the unit dose should be administered once a day. The experience with meropenem use in children with altered hepatic or renal function is extremely limited.

Adverse Effects

The most frequently related adverse events in meropenem are diarrhea, rash, nausea, vomiting and inflammation at injection site. Other reported adverse events are headaches, abdominal pain, oral thrush and mid prutitus. Drug related elevations in hepatic enzymes and thrombocytopenia has also been observed. Hematologic-agranulocytosis, neutropenia, and leukopenia. Skin "toxic epidermal necrolysis, Stevens-Johnson Syndrome, angioedema, and erythema multiform has also been reported after the use of Meropenem.

Seizures (overall seizure rate of (0.7%) and other adverse CNS experiences have been reported during treatment with Meropenem, most commonly in patients with preexisting CNS disorders (e.g., brain lesions or history of seizures) or with bacterial meningitis and/or compromised renal function. Anticonvulsant therapy should be continued in patients with known seizure disorders. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically, placed on anticonvulsant therapy if not already instituted, and the dosage of Meropenem re-examined to determine whether it should be decreased or the antibiotic discontinued. Meropenem appears to be well tolerated and is therefore safely used in meningitis. In patients with renal dysfunction, thrombocytopenia has been observed but no clinical bleeding reported. Meropenem may reduce serum valproic acid levels and sub-therapeutic levels may be reached in some patients.

Therapeutic Utility in Intensive Care Setting

Meropenem is most useful in treatment of serious bacterial infections including nosocomial in intensive care settings, specially in resistant and difficult-to-treat gram-negative infections. Its CSF penetrability and very low incidence of neurotoxicity makes it suitable for childhood meningitis. It can also be used as a monotherapy for treatment of infections in febrile neutropenic patients. As Meropenem is not effective against methicillin resistant staphylococci (including MRSA) and enterococcus, it should not be depended upon for treating suspected staphylococcal infections. Resistance to the tune of 12 percent has already been documented in Pseudomonas aeuruginosa strains isolated from hospitalized patients in India, therefore Meropenem should be used only for proven or strongly suspected infections caused by susceptible bacteria after relevant cultures has been taken.

Other carbapenems include Imepenem, artapenem and doripenem for gram–ve intra-abdominal and urinary tract infections.

LINEZOLID

The increasing resistance among gram-positive species is a major concern, because they are responsible for one-third of nosocomial infections. Methicillin-*resistant Staphylococcus aureus, Coagulase-negative staphylococcal species,* and *Enterococcus* are the most common nosocomial-acquired causes of bacteremia. Nearly 79 and 25 percent of nosocomially acquired, coagulase-negative staphylococcal species and *S. aureus* are methicillin-resistant, respectively. Worldwide emergence and rapid spread of community-acquired methicillin-resistant S. aureus has prompted a change in the approach to therapy of staphylococcal infections in both the outpatient clinic and the hospital.

Earlier Vancomycin was considered the final therapeutic option in cases in which enterococcus was resistant to all other antibiotics, but unfortunately, emergence of vancomycin-resistant enterococcus has been reported. In the community setting, the prevalence of drug-resistant *Streptococcus pneumoniae* has increased, often demonstrating intermediate or high-level resistance to penicillin or third-generation cephalosporins, respectively. Thus pneumococcal pneumonia is becoming more difficult to treat with first-line agents. Against this background, Linezolid belonging to a new class of antimicrobials called the oxazolidinones was developed primarily to fight resistant gram-positive cocci, such as *Vancomycin-resistant Enterococcus, Methicillin-resistant S. aureus, and Penicillin-resistant Pneumococci.*

Mechanism of Action

Linezolid disrupts bacterial growth by inhibiting the initiation process in protein synthesis. Linezolid prevents formation of the 70S ribosome complex that initiates protein synthesis by binding to the 23S subunit of the 50S subunit. Because of its unique binding site and its action at the early ribosome assembly step of protein synthesis, there is no cross resistance with other drug classes. This site of inhibition occurs earlier in the initiation process than other protein synthesis inhibitors (e.g., chloramphenicol, clindamycin, aminoglycosides, and macrolides) that interfere with the elongation process.[14] Because the site of inhibition is unique to linezolid, cross-resistance to other protein synthesis inhibitors has not yet been reported. Linezolid may also inhibit virulence factor expression and decrease toxin production in gram-positive pathogens. Linezolid is bacteriostatic against enterococci and staphylococci, and bactericidal for the majority of streptococci.

Pharmacokinetics

Linezolid is highly absorbed when administered orally, with a bioavailability of approximately 100 percent. This allows conversion from intravenous to oral therapy as soon as the patient is clinically stable; thus, it provides an advantage over comparative therapy that can be delivered only parenterally (i.e. vancomycin). Linezolid is metabolized via hepatic oxidation without any cytochrome P-450 pathways. Elimination occurs through nonrenal, renal, and fecal mechanisms accounting for 65, 30, and 5 percent, respectively. The half-life is approximately five hours. Generally, the dosing interval for an antibiotic is three times the half-life. The dosing interval for linezolid is every 12 hours. No dosage adjustment is recommended for patients with renal insufficiency; however, linezolid is removed by hemodialysis and should be administered following dialysis.

Indications

The FDA has approved linezolid for certain gram-positive infections in children. Other pathogens that linezolid has demonstrated in-vitro activity against include penicillin-resistant *S. pneumoniae,* vancomycin-sensitive *E. faecalis,* vancomycin-resistant *E. faecalis,* methicillin-susceptible *Staphylococcus epidermidis* and methicillin-resistant *S. epidermidis,* Corynebacterium sp, *Moraxella catarrhalis,* legionella species *Listeria monocytogenes, Pasteurella multocida,* and *Bacteroides fragilis.*[14,17]

Because of limited clinical data demonstrating activity against gram-negative organisms, it is recommended that coverage for these pathogens be added when indicated.

Therapeutic uses of Linezolid:

1. Vancomycin-resistant *Enterococcus faecium,* including cases with concurrent bacteremia
2. Nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and resistant strains) or *Streptococcus pneumoniae* (penicillin-susceptible strains only)

3. Complicated skin and skin structure infections caused by S. *aureus* (methicillin-susceptible and resistant strains), *Streptococcus pyogenes, Streptococcus agalactiae*
4. Uncomplicated skin and skin structure infections caused by S. *aureus* (methicillin-susceptible strains only) or S. *pyogenes*
5. Community-acquired pneumonia caused by S. *pneumoniae* (penicillin-susceptible strains only), including cases with concurrent bacteremia, or S. *aureus* (methicillin-susceptible strains only)

In a pediatric study the comparing Linezolid and Vancomycin (20 children treated with linezolid and 14 treated with vancomycin) in treatment of infections caused by MRSA the clinical cure rate was 94.1 percent in the linezolid group and 90.0 percent in the vancomycin group. Pathogen eradication rates were 88.2 and 90.0 percent for the linezolid and vancomycin groups, respectively. Fewer patients in the linezolid group had drug-related adverse events than did those in the vancomycin group.

Linezolid Dosing Recommendations

For children the recommended oral and parenteral dose is 10 mg/kg every 12 hours (Adults - 600 mg every 12 hours). Intravenous administration of drug should be done over 30-120 min. The duration of treatment for most of the infections like pneumonia including community acquired pneumonia and skin infections is 10-14 days. For Vancomycin resistant enterococcal infections therapy should be continued for 14-28 days.

Linezolid is available as 600 mg tablets, as parenteral formulations of 100 mL and 300 mL containing 2 mg/mL and oral suspension 20 mg/mL.

Linezolid is a pregnancy category C drug, and caution is urged if used in breastfeeding mothers because clinical data in pregnant women, or breastfeeding mothers are limited.

Adverse Effects

Adverse effects reported in clinical trials in more than 2 percent of patients include the following: rash, headache, diarrhea, nausea, vomiting, insomnia, constipation, and fever.[16] Thrombocytopenia was reported in 2.4 percent of patients receiving linezolid versus 1.5 percent in those in the comparator group. This effect may be associated with the higher dose or treatment duration exceeding two weeks.

Cases of myelosuppression (anemia, leukopenia, and pancytopenia) has been reported therefore monitoring of hematologic parameters is essential. Complete blood count should be monitored weekly, especially in patients receiving therapy longer than two weeks' duration, those with preexisting myelosuppression, those receiving drugs that produce bone marrow suppression, and those with a chronic infection who have received other antibiotic therapy recently or concurrently. If myelosuppression occurs, then discontinuation of therapy should be considered.

Drug-Drug Interactions

Linezolid does not affect cytochrome P-450; therefore, induced interactions are unlikely to occur. No pharmacokinetic interaction has been reported in patients taking warfarin or phenytoin. Linezolid is a reversible, nonselective inhibitor of monoamine oxidase (MOA), and a potential interaction with adrenergic or serotonergic agents is possible. A significant pressor response was observed when administered with tyramine; therefore, patients should avoid consuming food or beverages containing tyramine. More commonly used agents such as dopamine, epinephrine, or decongestants containing pseudoephedrine may also produce an exaggerated pressor response. Careful dosing titration is recommended when initiating dopamine or epinephrine. The potential for a serotonergic interaction with dextromethorphan was evaluated in healthy subjects. No serotonin syndrome effects (confusion, delirium, tremors, restlessness, hyperpyrexia, or diaphoresis) due to serotonergic interaction with dextromethorphan when administered together.

Incompatibilities

Incompatibilities with amphotericin B, ceftriaxone, chlorpromazine, diazepam, erythromycin, phenytoin, and trimethoprim-sulfamethoxazole have been reported. Because compatibility information changes, it is recommended that a pharmacist be consulted when there is doubt.

Clinical use

Linezolid should be reserved for the treatment of patients with infections caused by multidrug-resistant bacteria that are proved by laboratory testing, and to life-threatening or complicated infections associated with multiple resistances to first-line treatments. So far, it has demonstrated activity against all clinically significant, gram-positive bacteria. With its role in multidrug-resistant bacteria, linezolid will play a crucial role in both the community and the nosocomial setting. Physicians should prescribe this agent judiciously so as to minimize antimicrobial resistance.

TEICOPLANIN

Teicoplanin is a narrow spectrum antibiotic, which was formerly known as teichmycin A2. It belongs to group glycopeptides and resembles vancomycin in its structure. It interferes with cell wall synthesis by inhibiting polymerization of peptidoglycan.

Spectrum of Activity

Teicoplanin is active only against Gram-positive orga-nisms. It acts against both methicillin sensitive and methicillin resistant *Stapltylococcus aureus (S. aureus)*. It is as efficacious as vancomycin against these organisms. The efficacy of teicoplanin against *Staphylococcus aureus* can be improved by addition of aminoglycosides for synergistic effect. Teicoplanin is more efficacious than vancomycin for some of the streptococci especially enterococci. Teicoplanin is also effective against Listeria monocytogenes, *Corynebacterium spp., Clostridium spp.,* and anaerobic Gram-positive cocci.

Pharmocokinetics

Teicoplanin has bioavailability of 90-95 percent and its half-life is as long as 100 hours in patients with normal renal functions. Therefore, once daily dosage is sufficient for most of the infections. It is rapidly and extensively absorbed from muscle and peritoneal cavity, but very poorly from gastrointestinal tract. It penetrates slowly and poorly into cerebrospinal fluid. But relatively rapidly and effectively in synovial and pleural fluid and soft tissue. Its main route of excretion is through kidneys, so dosage needs to be modified in patients with renal insufficiency. In renal insufficiency, dose needs to be modified according to creatinine clearance. If creatinine clearance is less than 20 ml/min, dose should be reduced to 1/4th of the recommended dosage. If creatinine clearance is 20-50 ml/min. dose should be reduced to half.

Comparison of Vancomycin and Teicoplanin

Both these drugs have similar chemical structure, mechanism of action and clinical spectrum of activity. Teicoplanin has a longer half-life, so can be given once daily, whereas vancomycin needs to be given in 3-4 divided doses. Unlike vancomycin, teicoplanin can be used by intramuscular route. Teicoplanin is well tolerated intramuscularly for as long as 4 weeks.

Side Effects

Skin rash is the main side effect with teicoplanin. Liu et al have shown that vancomycin is more nephrotoxic than teicoplanin. Toxicological studies have shown that teicoplanin does not cause ototoxicity, whereas vancomycin is a potentially ototoxic drug. However, Bibler et al have reported an asymptomatic decrease in high frequency auditory threshold in one patient, one week after discontinuation of teicoplanin.

Dagon, et al used teicoplanin in 64 children and observed transient decrease in white blood cell count in 4 patients, elevation of liver transminase in 3 patients and elevation of creatinine in 1 patient. All these side effects were mild and transient and did not necessitate cessation of therapy. Drug fever, hypersensitivity reactions, eosinophilia and bronchospasm are other side effects reported with teicoplanin. In some individuals, teicoplanin can cause mild long-lasting pain at the site of injection. Catheter related phlebitis is unusual with teicoplanin, whereas it is a common occurrence with vancomycin.

Therapeutic Uses

Teicoplanin can be used for methicillin sensitive as well as methicillin resistant *Staphylococcus aureus*. Dagon et al have concluded from their study that teicoplanin is a safe and efficacious drug for outpatient and inpatient treatment of serious Gram-positive infections in children including *S. aureus* and *Streptococcus pyogenes*.

Resistance of *S. aureus* to teicoplanin has been reported during therapy of endocarditis. The exact mechanism of this resistance is not clear, but this resistance was not plasmid mediated and was also not associated with changes in the cytoplasmic membrane proteins.

Goldstein et al studied the distribution of teicoplanin and vancomycin resistant strains among coagulase negative staphylococci (CONS) and have shown that teicoplanin is less effective than vancomycin against CONS and the most resistant strain is *S. hemolyticus.* Del Alamo et al also studied antimicrobial susceptibility of 239 CONS from blood cultures. In their study, teicoplanin resistance was found in 9 isolates. However, these isolates remained susceptible to vancomycin. These studies suggest that teicoplanin is an effective drug for CONS, however, resistance is more common with teicoplanin as compared to vancomycin.

Teicoplanin is an effective drug for serious entercoccal infections. However, it should be combined with aminoglycosides for bactericidal action.

Dosage and Formulation

The recommended dosage of teicoplanin by manufacturer is 10 mg/kg by intravenous route every 12 hourly for first three doses, then 6 mg/kg/day by intramuscular or intravenous route. For neonates, dosage is 16 mg/kg for first day followed by 8 mg/kg/day and dosage should be given as intravenous infusion over 30 minutes.

Teicoplanin is available as Targocid in 200 mg and 400 mg vials by Hoechst Marion Roussel Company. The cost of 200 mg via is Rs. 730 and 400 mg vial is Rs. 1200. Oral preparation of teicoplanin is not available in India.

TIGECYCLINE

Tigecycline can be used as an empiric monotherapy to treat a variety of abd/skin soft tissue infections, both hospital- and community-acquired (e.g. complicated appendicitis, infected burns, intra-abdominal abscesses, deep soft tissue infections, and infected ulcers).

Microbiology

Tigecycline, a glycylcycline, inhibits protein translation in bacteria by binding to the 30S ribosomal subunit and blocking entry of amino-acyl tRNA molecules into the A site of the ribosome. This prevents incorporation of amino acid residues into elongating peptide chains. Tigecycline carries a glycylamido moiety attached to the 9-position of minocycline. The substitution pattern is not present in any naturally occurring or semisynthetic tetracycline and imparts certain microbiologic properties to tigecycline. Tigecycline is not affected by the two major tetracycline resistance mechanisms, ribosomal protection and efflux. Accordingly, tigecycline has demonstrated in vitro and in vivo activity against a broad spectrum of bacterial pathogens. There has been no cross resistance observed between tigecycline and other antibiotics. Tigecycline is not affected by resistance mechanisms such as beta-lactamases (including extended spectrum beta-lactamases), target site modifications, macrolide efflux pumps or enzyme target changes (e.g. gyrase/topoisomerase). In vitro studies have not demonstrated antagonism between tigecycline and other commonly used antibacterial drugs. In general, tigecycline is considered bacteriostatic.

Tigecycline Antibacterial Spectrum

Tigecycline has been shown to be active against most strains of the following microorganisms:

Aerobic and facultative Gram-positive microorganisms

Enterococcus faecalis (vancomycin-susceptible isolates only)
Staphylococcus aureus (methicillin-susceptible and -resistant isolates)
Streptococcus agalactiae
Streptococcus anginosus grp. (includes *S. anginosus, S. intermedius,* and *S. constellatus*)
Streptococcus pyogenes

Aerobic and facultative Gram-negative microorganisms

Citrobacter freundii
Enterobacter cloacae
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Anaerobic microorganisms
Bacteroides fragilis
Bacteroides thetaiotaomicron
Bacteroides uniformis
Bacteroides vulgatus
Clostridium perfringens
Peptostreptococcus micros

Not Good For Pseudomonas

Patients with severe hepatic impairment should be treated with caution and monitored for treatment response.

Dose

The recommended dosage regimen for Tigecycline is an initial dose of 100 mg, followed by 50 mg every 12 hours. Intravenous (IV) infusions of Tigecycline should be administered over approximately 30 to 60 minutes every 12 hours.

The recommended duration of treatment with Tigecycline for complicated skin and skin structure infections or for complicated intra-abdominal infections is 5 to 14 days. The duration of therapy should be guided by the severity and site of the infection and the patient's clinical and bacteriological progress.

Colistin (polymyxin E) is an antibiotic effective against Pseudomonas, Acenitobacter Aerosolized colistin has been used but is not good for asthma (can induce bronchospasm) there is no pediatric data regarding use of colistin.The main adverse effect of treatment was renal failure; 27 percent of patients with initially normal renal function had renal failure, and renal function worsened in 58 percent of patients with abnormal baseline creatinine levels. Colistin may still be a good therapeutic option for the treatment of severe infections caused by multidrug-resistant *P. aeruginosa.*

Empirical Use of Anti-Fungal Agents in Severe Sepsis or Septic Shock Empirical antifungal therapy should not be used on a routine basis in patients with severe sepsis or septic shock, but it may be justified in selected subsets of septic patients at high risk for invasive candidiasis
Grade E

Liposomal Amphotericin Nephrotoxicity and infusion-related reactions are frequent adverse events of treatment with amphotericin B deoxycholate, and treatment interruptions because of toxicity may have a negative impact on efficacy.

Infusion-related reactions were significantly less frequent with liposomal amphotericin B (5% to 20%) than with amphotericin B lipid complex (40% to 80%) or colloidal dispersion of amphotericin B (50% to 80%). Therefore, liposomal amphotericin B has been used as the control treatment regimen in most recent studies of empirical antifungal therapy for persistent fever in neutropenic cancer patients.

Lipid Formulations of Amphotericin B:

Three preparations are available:

1. Liposomal amphotericin B,
2. Amphotericin B lipid complex, and
3. Amphotericin B colloidal dispersion. They have been primarily used for the treatment of cancer patients with neutropenia and persistent fever or with invasive aspergillosis. Lipid formulations are considerably more expensive than conventional amphotericin B, which has had a negative impact on their use.

Newer antifungal agents: Itraconazole An azole with improved in vitro activity against fluconazole-resistant Candida species. However, a poor bioavailability of the oral formulation of Itraconazole has been a major limitation for its use in critically ill patients. Recently, an intravenous form of itraconazole has been developed, but there are very few data on the efficacy of IV Itraconazole for the treatment of candidemia.

Voriconazole A member of the newest generation of antifungal triazoles, has been shown to exhibit excellent in vitro and in vivo activities against Candida species In patients with oropharyngeal and/or esophageal candidiasis, voriconazole was found to be at least as effective as fluconazole

Voriconazole A large multicenter study comparing voriconazole with sequential use of amphotericin B deoxycholate followed by fluconazole in non-neutropenic patients with candidemia has recently been completed, and the first results of that trial indicate that voriconazole is as effective as and was better tolerated than amphotericin B/fluconazole.

Echinocandins (Caspofungin) In a large multicenter adult trial that included caspofungin (70-mg loading dose, followed by 50 mg daily) was at least as efficacious as and less toxic than amphotericin B deoxycholate (0.6-1.0 mg/kg/day) Anidulafungin is a newer echinocandins that is available now for clinical use. Posaconazole and Ravuconazole are two other triazoles in clinical development.

SUMMARY RECOMMENDATIONS

Antimicrobial therapy for patients with severe sepsis and septic shock: An evidence-based review

- Critical Care Medicine: Volume 32(11) Supplement November 2004 pp S495-S512
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1. Antibiotic therapy should be started within the first hour of recognition of severe sepsis, after appropriate cultures have been obtained. Recommendation: Grade E
2. Initial empirical antiinfective therapy should include one or more drugs that have activity against the likely pathogens (bacterial or fungal) and that penetrate into the presumed source of sepsis. The choice of drugs should be guided by the susceptibility patterns of microorganisms in the community and in the hospital. Recommendation: Grade D
3. Monotherapy is as efficacious as combination therapy with a β-lactam and an aminoglycoside as empirical therapy of patients with severe sepsis or septic shock.Recommendation: Carbapenem: Grade B. Third- or fourth-generation cephalosporins: Grade B. Extended-spectrum carboxypenicillins or ureidopenicillins combined with β-lactamase inhibitors: Grade E.
4. Third-generation and fourth-generation cephalosporins, carbapenems, and extended-spectrum carboxypenicillins or ureidopenicillins combined with β-lactamase inhibitors are equally effective as empirical antibiotic therapy in patients with severe sepsis.
   Third- or fourth-generation cephalosporins: Grade A.
   Carbapenem: Grade B.
   Extended-spectrum carboxypenicillins or ureidopenicillins combined with β-lactamase inhibitors: Grade C
5. Empirical use of glycopeptide antibiotics (vancomycin, teicoplanin), oxazolidinones (linezolid), or streptogramins (quinupristin/dalfopristin) in patients with severe sepsis or septic shock is justified in patients with hypersensitivity to β-lactams or in institutions with resistant Gram-positive bacteria (i.e. methicillin-resistant staphylococci, penicillin-resistant pneumococci, or ampicillin-resistant enterococci) in the community or in the hospital.Recommendation: Grade E.
6. Modification of empirical antimicrobial therapy with the aim to restrict the number of antibiotics and narrow the spectrum of antimicrobial therapy is an important and responsible strategy for minimizing the development of resistant pathogens and for containing cost. Grade E.
7. The antimicrobial regimen should always be reassessed after 48-72 hrs on the basis of microbiological and clinical data with the aim to use a narrow-spectrum antibiotic to prevent the development of resistance, to reduce toxicity, and to reduce costs. Once a causative pathogen is identified, there is no evidence that combination therapy is more effective monotherapy. The duration of therapy should typically be 7-10 days and guided by clinical response. Grade E.
8. If the presenting clinical syndrome is determined to be due to a noninfectious cause, antimicrobial therapy should be stopped promptly to minimize the development of resistant pathogens and superinfection with other pathogenic organisms. Grade E.
9. At the present time, there is insufficient evidence to recommend the use of antibiotic cycling as a strategy to reduce the development of antibiotic resistance. Grade C
10. Empirical antifungal therapy should not be used on a routine basis in patients with severe sepsis or septic shock, but it may be justified in selected subsets of septic patients at high risk for invasive candidiasis .Grade E.
11. Azoles (fluconazole) and echinocandins (caspofungin) are as efficacious as and less toxic than amphotericin B deoxycholate for the treatment of patients with candidemia. Albeit better tolerated, there is no evidence that lipid

formulations of amphotericin B are superior to amphotericin B deoxycholate for the treatment of candidemia.

- Azoles: Grade A.
- Echinocandins: Grade B.
- Lipid formulations of amphotericin B: GradeE

The strength of the recommendations

- A: Supported by at least two level I investigations
- B: Supported by only one level I investigation
- C: Supported by level II investigations only
- D: Supported by at least one level III investigation
- E: Supported by level IV or level V investigations only

Evidence-Based Medicine Working Group. Evidence-based medicine: A new approach to teaching the practice of medicine. JAMA 1992; 268:2420-2425.

SUMMARY

It should be routine to send blood or relevant tissue fluid culture before starting antibiotics empirically. However, once drug sensitivity is known, even when patient is improving on chosen antibiotic, step down alternative must be considered if possible. Antibiotic policy has to be decided by individual units based on local epidemiology. But broad principles can be implemented. It is important to avoid antibiotics for non-infectious illness and not to treat leucocytosis or low grade fever with antibiotics. Positive cultures from nonsterile sites should be disregarded. Quantitative cultures may help to distinguish between colonization from infection. Undrained abscess and collection of pus or retained foreign body need proper action and not just antibiotics. It is ideal to de-escalate broad spectrum therapy once sensitivity pattern is known. Resistance to antibiotics correlates with duration of exposure and probable underdosing. Patients already on antibiotics run higher risk of developing resistant nosocomial infection as happens commonly in ventilator associated pneumonia. Reduction of duration of antibiotics for postoperative prophylaxis and also for patients with unconfirmed infections help in control of resistant infections. "Antibiotic cycling" may be a solution but cycle timing and choice of antibiotics need to be researched. Even in case of successful empirical treatment, narrow spectrum antibiotic may be chosen based on culture results. This will save problems of resistance. Antibiotic use needs cautious approach. Prevention of infection by every other possible measures is the key to aovid drug resistance.

FURTHER READING

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CHAPTER

82

Nosocomial Infection and its Management

Soonu Udani

Hospital-acquired infections or nosocomial infections (NI) encompasses any infection that is neither present, nor incubating on hospital admission.[1] They encompass almost all clinically evident infections that do not originate from the patient's original admitting diagnosis. Nosocomial infections are caused by viral, bacterial, and fungal pathogens. The likelihood of occurrence of NI is 6 percent with each day spent in the hospital and probably more in the ICU setting.[2] An analysis on the impact of NIs on health care reveals that they are responsible for morbidity, mortality, length of ICU and hospital stay and over utilization of resources.

Antimicrobial therapy for NIs has become complicated due the high level of antibiotic resistance encountered. Changing patterns of resistance and of microbial flora in hospitals need the clinician to be highly aware of current trends in treatment. It cannot be stressed enough that no textbook recipe will apply to every hospital or clinical setting. Local patterns of resistance and of microbial flora are two key determinants of both, empiric and definitive treatment.

Risk Factors: (2) The APACHE and PRISM scores were designed to predict mortality and are less consistent predictors of NI. The 3 major factors are 1) prolonged stay 2) Mechanical ventilation (MV) and 3) vascular access. Among other factors are:

1. Shock on admission
2. More than 10 beds in a unit
3. Parenteral nutrition
4. Empirical antibiotic therapy
5. Tracheostomy
6. ICP monitoring
7. Poor nurse to patient ratio

Understaffing and overcrowding in ICUs have been reported to increase the risks of human error, iatrogenic complications and even death.[3] NIs now concern 5-15 percent of hospitalised patients and can lead to complications in 25-33 percent of those patients admitted to ICUs. The most common are pneumonias in ventilated patients and bacteremia derived from intravascular catheters.[2] Accordingly, infection control measures are to be viewed as a priority and have to be integrated fully into the continuous process of improvement of the quality of care.

Pathophysiology: The colonization of the host by potentially pathogenic microorganisms is a prerequisite for the further development of NIs and may occur from endogenous or exogenous flora. Critically ill patients are particularly susceptible to rapid colonization by endemic pathogens from the hospital environment. The endemic transmission of exogenous staphylococci and other pathogens by the hands of health care workers (HCWs) may seem obvious but is also well documented. Goldman reported the presence of Gram-negative bacilli on the hands of 75 percent of neonatal ICU personnel.[4] The hands of HCWs are only transiently contaminated and proper washing is sufficient to remove the organisms and stop transmission.

Many NIs are believed to arise from the endogenous flora of the skin, GI tract or oropharynx. Steroids, chemotherapy and antibiotics along with invasive devices like central and arterial lines, gastric tubes and urinary catheters play a role.

Nosocomial invasive bacterial and fungal infections cause:

- Bloodstream infections
- Ventilator-associated pneumonia (VAP)
- Urinary tract infection (UTI)
- Lower respiratory infection
- Gastrointestinal, skin, soft tissue, and cardiovascular infections
- Surgical-site infections
- Ear, nose and throat infections

An Indian study showed that 33 percent of infections were from Klebsiella and the most common site was the urinary tract (56.5%).[5]

Microbiology: A continuous shift towards more resistant bacteria has been reported over the last several decades. The predominant organisms reported from hospitals all over the world are Coagulase negative Staphylococci, *P aeruginosa,* Enterococci and Candida.

The factors responsible are not fully understood but **antibiotic pressure** plays a significant role. Antibiotic exposure, especially with the cephalosporins, constitutes an independent risk factor for NI with resistant Gram positive cocci and gram-negative bacilli.[6] That prophylaxis with cephalosporins for even <48 hours is associated with an increased incidence of colonization with resistant Gram-negative bacteria was shown by Harbarth et al.[7]

Main Pathogens responsible for NIs: NNIS.[6] Antibiotic Resistance in ICUs surveillance report 1999 December.

[illegible]	[illegible]	[illegible]
CoNS/methicillin	52.3	37
S aureus/methicillin	87	2
Enterococci/vancomycin	25.2	43
E coli/3 gen cephalosporin	8	3
Enterobacter/3 gen cephal	34	-4
K.pneumoniae/3 gen cephal	10	-3
Pseudomonas/Imipenem	56	21.4
Pseudomonas/Quinolones	23.2	30.2

The Changing Face of NIs

The growing incidence of gram- negative organisms, overtaking the Gram positive ones is described all over the world. Our own hospital data confirms the situation to be no different in India:

In the setting of widespread prevalence of ESBL (extended spectrum beta lactamase) and Amp C producing gram negative bacilli in ICU's carbapenems are being increasingly used. Evidence that "Inappropriate initial therapy is associated with increased mortality" has lead to indiscriminate empirical use of carbapenems. The fallout has been an increase in the prevalence of multi drug and carbapenem resistant, or so called XDR strains of *P. aeruginosa* (45% at Hinduja Hospital) and Acinetobacter species. The prevalence of these XDR strains in the ICU of the authors institution is 45 percent pseudomonas an (termed as XDR strains, 40% in Hinduja Hospital, unpublished data). Resistance in these organisms to carbapenems is a consequence of increased drug pressure and is due to combination of various mechanisms including carbapenemases, multi drug efflux pump and loss of porin channels. Therapeutic options for these XDR isolates is colistin (an expensive, not easily available and toxic drug) and sometimes if one is lucky chloramphenicol. Restricting the use of carbapenems to only very sick patients, rapid deescalation once culture reports come in and prevention of clonal spread of these organisms in the ICU by good infection control measures are vital to counter this problem.

The rising incidence of Gram-negative pathogens is accompanied by a serious problem of resistance.

The MRSA surveillance study group,[8] reported an overall 31.8 percent resistance of S Aureus to Methicillin, from all over the country.

The emergence of Enterococci as a dominant pathogen is also alarming. Till date we have not encountered any Vancomycin resistance, but VRE[6] (vancomycin resistant Enterococci) have been reported from several countries.

Nosocomial Fungal Infections

Candida has emerged as an important nosocomial pathogen in recent years. Both candida albicans and non albicans candida are implicated. Risk factors for invasive candida infections in ICU's include prolonged antibiotic therapy, very low birth weight infants, surgery (particularly gut surgery), presence of a central venous catheter, intravenous alimentation, and prolonged ICU stay. Therefore in the event of nosocomial sepsis in these settings the possibility of fungal infection should be considered and fungal cultures be sent. Empirical antifungal therapy may be started in sick patients till cultures are available as time of initiation of antifungal therapy is an important determinant of mortality and because fungal cultures may be positive in only 50 percent of invasive fungal infections. Options for empirical therapy are fluconazole, amphotericin B and now caspofungin. Choice depends on the degree of sickness, whether the patient was on fluconazole prophylaxis and the prevalence of azole resistance candida in the local setting. Studies have shown that antifungal prophylaxis with fluconazole/ketoconazole in patients with risk factors for fungal infections significantly reduces invasive fungal infections and mortality but may increase colonization with azole resistant candida.

Ventilator Associated/Intubation Associated or Hospital Acquired Pneumonias (VAP/IAP/HAP)

Definition (2): New or increased production of purulent sputum and/or a fever of >38°C with clinical signs (rales, bronchial breath sounds, dullness to percussion) and/or chest radiographs showing new or progressive infiltrates, consolidation, cavitation or pleural effusion not attributable to any other disease process.

VAP: New radiographic infiltrate + at least 2 of the following: fever >38°/<35°; leukocytosis/leukopenia; purulent sputum; isolation of pathogenic bacteria from the lower respiratory tract.

The most common organism still remain Pseudomonas aeruginosa.[9] This is the experience in the author's hospital as well:

Usual Organisms

1. *Pseudomonas aeruginosa*
2. *St aureus* (MRSA)
3. *Enterobacter / Enterococci*
4. *Klebsiella*
5. *H influ*
6. *E Coli*

Fungus

Incidence: Seen in 9- 21 percent of MV patients. Adult units report higher figures than PICUs(NNISS). If only 1 percent of all hospitalized patients are ventilated and if 17 percent of all pneumonias occur in these patients, the role of MV is obvious. 70 percent of patients who die of ARDS show changes of infection at autopsy.

Chest X-rays can be deceptive as many other conditions in critically ill patients can mimic pneumonic patches:

1. Pulmonary edema
2. Thromboembolism
3. Drug reactions
4. Pulm hemorrhage
5. Alveolitis
6. ARDS

Blood cultures in VAPs are only positive in 8 - 20 percent of patients. They indicate an increased risk of having a complicated course and when two pathogens are isolated it usually means an infection at an extrapulmonary site e.g. line sepsis.

Clinical criteria alone are not enough to diagnose VAP. Fever, leukocytosis and other features of "sepsis" coexist in most patients for various reasons. New infiltrates on the chest X-ray are certainly important, especially if there was no lung pathology earlier.

Isolates from the tracheo-bronchial tree are important for the diagnosis as well as selection of antibiotic.

Quantitative cultures of ET aspirates (ETA): Besides oropharyngeal colonizers, unprotected ETA will invariably yield Pseudomonas, Klebsiella, Staphlococci, Candida and other organisms that have transmigrated or overgrown from selective antibiotic pressure.

These therefore have to be looked at in the light of the presence of WBCs, macrophages in the smear, and quantitative cultures. Colony counts of >10^4-10^5 CFU/ ml have a specificity of >70 percent. The growth of multiple organisms should also be taken with some skepticism.

Endotracheal Aspirates advantages and disadvantages:

- Easy
- False positivity very high
- Quantitative with 10^6 CFU/ml better
  - Available within 24 hours
  - Compare OK with PBB

1. Result in over treatment

Quantitative cultures with protected brush biopsy: (PBB)[10]: the yield here is more specific with a nonbronchoscopy distal protected brush. Bronchoalveolar lavage (BAL) provides immediate visualisation of intra/extra cellular bacteria on smears but is rarely available to small children. PBB + BAL + exam of BAL fluid, increases the sensitivity to almost 96 percent as compared to 83 percent with ETAs and colony counts.

Methods of preventing VAPs: Still the most important and possibly the most difficult aspect of VAPs

Proven value:

1. Cleaning protocols for tubing (disposable whenever possible)
2. Strict sterile precautions during suctioning,
3. Closed system suction whenever possible,
4. Postural drainage, Chest physiotherapy,
5. Patient triggered modes and avoidance of paralysis to keep reflexes as intact as possible

May warrant consideration:

1. Eradication of the ETT biofilm by nebulised antibiotics: A recent study by Adair, demonstrated that patients treated with nebulised Gentamicin showed colonization only with "normal' oropharyngeal flora, while those nebulised with a cephalosporin showed colonization and VAPs with Staphlococci, enterococci, pseudomonads.[11]
2. Avoid overuse of H2 receptor blocking agents to reduce acid production. This changes the flora and allows transmigration.
3. NG tubes may increase reflux and aspiration
4. Decontamination of the subglottic region by continuous antibiotic infusion.Normal people frequently aspirate oropharyngeal secretions during sleep but host defenses prevent lung infection and the type of organisms are less virulent. In non-hospitalised patients being treated with H2 blockers, gram positive organisms predominate whereas in hospitalized patients aerobic gram negative organisms are predominant.[12]

Sources of microorganisms may be endogenous or exogenous.

Endogenous	Exogenous
Nasal carriers	Health care workers
Sinusitis	Ventilator circuits
Oropharynx	Nebulisers
Trachea	Biofilms
Gastric juice	
Leads to----Aspiration	Inhalation-----leads to

Sinusitis without HAP can be a source of fever in the PICU. In children this possibility is often ignored. Nasotracheal intubation(42% vs 6% for oral)[13] and prolonged nasogastric tubes in situ may contribute to poor drainage and resulting infection.

According to a meta-analyses of the efficacy of stress ulcer prophylaxis in ICU patients, HAPs were significantly lower in those receiving sucralfate than in those receiving agents that reduced gastric pH.[14]

Despite advances in antimicrobial therapy, the treatment of HAPs remains unsatisfactory, as the entire diagnostic process is fraught with inaccuracies and pitfalls. All efforts to pinpoint an accurate diagnosis are expensive, technically difficult and require time. Whereas the survival of the patient may well depend on rapid and correct administration of an appropriate agent. This was shown in a study by several investigators.[15,16] The mortality rates were considerably higher for those where the first choice of antibiotic proved to be incorrect.

Two factors seem to render the choice of antibiotics particularly difficult in the PICU. First, HAPs are likely to result from highly resistant organisms, as most patients are treated with antibiotics. Second, multiple organisms are very often cultured from the respiratory secretions of these patients. Because of the emergence of multi resistant, extended spectrum β lactamase producing (ESBL) Gram negative organisms and the increasing role played by MRSA, even a protocol combining Ceftazadime or Imipenum and Amikacin might not ensure adequate coverage. Finally, although appropriate antibiotics will surely improve survival of those with true HAPs, use of broad spectrum empiric antibiotics in patients without infection or with infections caused by susceptible microorganisms, has the tremendous potential to disseminate the growth of multi resistant colonizers and superinfectors, which will then pose an immediate and remote danger to current and future patients. This aspect and very real danger should be made clear to every physician treating patients in the neonatal and pediatric ICU.

Catheter Related Blood stream infections(CRBSIs): Primary blood stream infection refers to a bacteremia or fungemia for which there was no documented distal source. It includes peripheral IV, arterial and all central lines.[2]

Although not necessarily more lethal, these infections are somehow dreaded more than VAPs. If the host is recovering and the organism is sensitive to available antibiotics, recovery is usual. The problem of obtaining positive blood cultures on a patient already on antibiotics, often forces us to start and continue empirical treatment according to our own local sensitivity and organism patterns. Hence the knowledge of local problems is extremely important. As in VAPs, CRBSIs are often a diagnostic problem. Once again, leukocytosis, fever, and other tell tale signs are commonly present. The problem is easier if there is a recrudescence of fever after an afebrile period or if the WBC counts were normal and then show a rise. Discordant results from cultures drawn simultaneously from different lumens occurred in 13 (32%) of 41 episodes. The estimated sensitivity of a culture drawn from a single lumen was 84 percent in one study.[17] Drawing blood cultures from all lumens of these lines should be considered. Cultures drawn from central lines may indicate colonization only. Concomitant peripheral cultures should be drawn to reinforce a positive line culture.

Nosocomial etiologies in bloodstream infections include the following:[7]

- Coagulase-negative staphylococci, 40 percent
- Enterococci, 11.2 percent
- Fungi, 9.65 percent
- *Staphylococcus aureus*, 9.3 percent
- *Enterobacter* species, 6.2 percent
- Pseudomonads, 4.9 percent

The percentages are from the US based NSSI. These will be different in every country and city.[18]

Catheter Venous Catheter (CVC) Related Infections/Blood Stream Infections (CRBSI)

The use of short or long term indwelling catheters is no longer restricted to the intensive care units. Oncologists and surgeons often treat or even discharge home, children with indwelling lines or ports. CVC related infections include exit, tunnel, pocket and Ca-BSIs. Whereas local signs will characterize the first three, the last needs to be accurately diagnosed for appropriate management.

The most accurate diagnosis of a CRBSI is made when there is an incremental increase in the quantity of bacteria from blood obtained through the catheter compared to that obtained from a peripheral puncture[19] due to the cost and non-availability of this method, the less specific method of two simultaneous blood cultures; one from the catheter and one from the periphery-both growing the same organisms, especially in the presence of fever, is taken as evidence of a CRBSI. In adult populations, it is recommended that non-tunneled catheters should be removed.[1] However, this may not always be feasible in the neonatal and Pediatric populations. While all catheters showing local infection must be removed, successful treatment of CRBSI without catheter removal have been recorded but treatment may depend on the pathogen identified.[20]

Pathogen Specific Treatment

Coagulase negative Staphlococcus (CoNS): This is the commonest and least virulent organism, with less sepsis and rarely a poor outcome. Pulling the catheter may solve the problem. A short course of 3-5 days of Kloxacillin may be appropriate in newborns and immunocompromised patients. Ist generation cephalosporins and Amoxy-Clav will also work but these have a broader spectrum than Kloxacillin and hence this is the first choice.[21] If the catheter remains in place, 10-14 days of treatment after a negative blood culture is recommended. If the blood culture remains positive on 3 occasions or if the child continues to have systemic signs of infection, the catheter should come out.[22] However, relapses are more frequent (20%) when the catheter is kept in situ as compared to when it is removed(3%)[23] *Staphylococcus aureus*: This is a more virulent pathogen whether it is sensitive or resistant to Methicillin. Serious systemic infection, seeding to organs and joints and even endocarditis occur. The patient is better off without the catheter. Two weeks of appropriate antibiotics according to sensitivity is needed.[1] If the pathogen is Methicillin resistant(MRSA) then IV Vancomicin is the usually chosen drug. The dose ranges from 30-60mg/k/day divided 8 hourly, adjusted for gestational age and renal clearance. Monitoring of levels is highly desirable. Teicoplanin may be a substitute if iv therapy has to be changed to once a day dosing or itramuscular. The frequently asked question here is always about Linezolid, orally administered without levels being monitored. For initial therapy, only the iv route is acceptable. Once cultures revert to negative, oral therapy may be given. In a study on neonates with varing infections, clinical cure rates at follow-up in the intent-to-treat group were higher, but not significantly different, for linezolid vs. vancomycin (78% vs. 61%; P = 0.196). Fewer linezolid-treated neonates had drug-related adverse events than vancomycin-treated neonates.[24] Conventional wisdom cautions against the serial use of different drugs. In practice, because of its better tissue concentration, we restrict the use of Linezolid for deep soft tissue infections, empyemas, pneumonias or long term therapy.

Fungal: Most *Candida albicans* will be sensitive to Fluconalzole. Candida species or other fungi may require specific testing or if not available, Amphotericin B will have to be used. For simple CRBSI, after pulling the catheter, two weeks will be sufficient. However, a diligent search needs to be made in the eyes, liver, urinary tract and bones and joints (if symptoms suggest), as treatment will then be more prolonged. Dissemination occurs in 17 percent and mortality may be as high as 20 percent.[25]

Risk Factors for CRBSIs

Central lines vs peripheral lines: 90 percent of BSIs are from central lines[5]
Multilumen catheters[26]
Experience prevents contamination during insertion
Transparent dressings that allow moisture to be trapped may increase colonization[27]
Poorly handled lines, TPN solutions, lipid emulsions
HAND WASHING protocol lapses
Chlorhexidine gluconate versus povidone-iodine for insertion-site skin disinfection.[28]

Millions of dollars have been spent on finding the ideal substance which will prevent colonization of central venous catheters. No chemical or antibiotic has emerged as ideal and the cost of these catheters is still very high. A combination of silver sulphadine and chlorhexidine (SSC) demonstrated a longer colonization free interval of about 21 days when compared to a combination of Minocycline and rifampicin (M+R), which proved effective for about 3 days.[29] Obsessive infection control practices, adherence to protocols, and restricted antibiotic usage today are the time tested method of preventing CRBSIs.

Catheter associated UTIs: (CAUTI) Probably the most frequently used indwelling catheter is the urinary catheter in the bladder. Rates of infection are directly proportional to the time the catheter is in place. Pediatric patients have a cumulative risk of a UTI of 30 percent when catheterized.[30] The infant or newborn is at higher risk even without catheterization and is also more prone to develop a blood stream infection. Once again, the problem remains of infection vs colonization. Protocols for catheter care are also useful in reducing infections. The patient's own gut flora is usually responsible, but indirectly, hospital flora are encountered, as the patient's own flora gets replaced very quickly by pathogens prevalent in the unit.
Nosocomial etiologies in UTI include the following:

1. Gram-negative enterics, 50 percent
2. Fungi, 25 percent
3. Enterococci, 10 percent

A fundamental question here is whether all urinary cultures from indwelling catheters should be taken as infections and treated.

Diagnosis of CAUTI:[31]
Without an indwelling catheter:
Clean catch mid stream urine growing > 10^5 bacteria /ml
Any growth from a suprapubic specimen
With an indwelling catheter:
Bacterial counts of $>10^2$/ml in aspirates from the catheter from the port.

For either short- or long-term catheters, the infection rate is about 5 percent per day. Escherichia coli remains the most common infecting organism, but a wide variety of other organisms may be isolated, including yeast species. Bacteria tend to show increased resistance because of the repeated antimicrobial courses. Urinary tract infection (UTI) usually follows formation of biofilm on both the internal and external catheter surface. The biofilm protects organisms from both antimicrobials and the host immune response. Morbidity from UTI with short-term catheter use is limited if appropriate catheter care is practised. In patients with long-term catheters, fever from a urinary source is common with a frequency varying from 1 per 100 to 1 per 1000 catheter days. Asymptomatic catheter-acquired UTI should not be treated with antimicrobials.

Antimicrobial treatment does not decrease symptomatic episodes but will lead to emergence of more resistant organisms. For treatment of symptomatic infection, many antimicrobials are effective. Wherever possible, antimicrobial selection should be delayed until culture results are available. Whether to administer initial treatment by an oral or parenteral route is determined by clinical presentation. If empirical therapy is required, (though best avoided) antimicrobial selection is based on variables such as route of administration, anticipated infecting organism and susceptibility, and patient tolerance. Renal function, concomitant medications, local formulary and cost may also be considered in selection of the antimicrobial agent. The duration of therapy is usually 10-14 days, but patients who respond promptly and in whom the catheter must remain in situ may be treated with a shorter 7-day course to reduce antimicrobial pressure. Relevant clinical trials are necessary to define optimal antimicrobial regimens for the management of catheter-acquired UTI. Prevention of catheter-acquired UTI and its complications is a major goal. With short-term catheters, avoiding their use or limiting the duration of use to as short a time as possible are the most effective prevention strategies. Maintaining a closed drainage system and adhering to appropriate catheter care techniques will also limit infection and complications. As the duration of catheterisation is the principal determinant of infection with long-term indwelling catheters, it is not clear that any interventions can decrease the prevalence of bacteriuria in this setting. Catheter flushing or daily perineal care do not prevent infection and may, in fact, increase the risk of infection. Complications of infection may be prevented by giving antibacterials for bacteriuria immediately prior to any invasive urological procedure, and by avoiding catheter blockage, twisting or trauma. The major focus of future advances in prevention of catheter-acquired UTI is the development of biomaterials resistant to biofilm formation. There is substantial current research addressing this issue, but current catheter materials all remain susceptible to biofilm formation.[32]

Infection Control

Three decades ago infection control, programs were created to control antibiotic resistant nosocomial infections, but the numbers of these infections have continued to increase, leading some to question control is feasible. MRSA and VRE continued to appear despite antibiotic policies, control and surveillance.

Surveillance

Routine surveillance cultures do not reduce NI, nor do they replace good clinical practice of hand washing and infection control. Awareness of loacal and in hospital trends of pathogens and sensitivity patterns is vital. Timely indentification of NI and containment of spread is virtal. The CDC has guidelines, protocols and definitions for institutions. The Hospital Infection Society of India also has practical guidelines that may be of use to our smaller institutions and nursing homes.

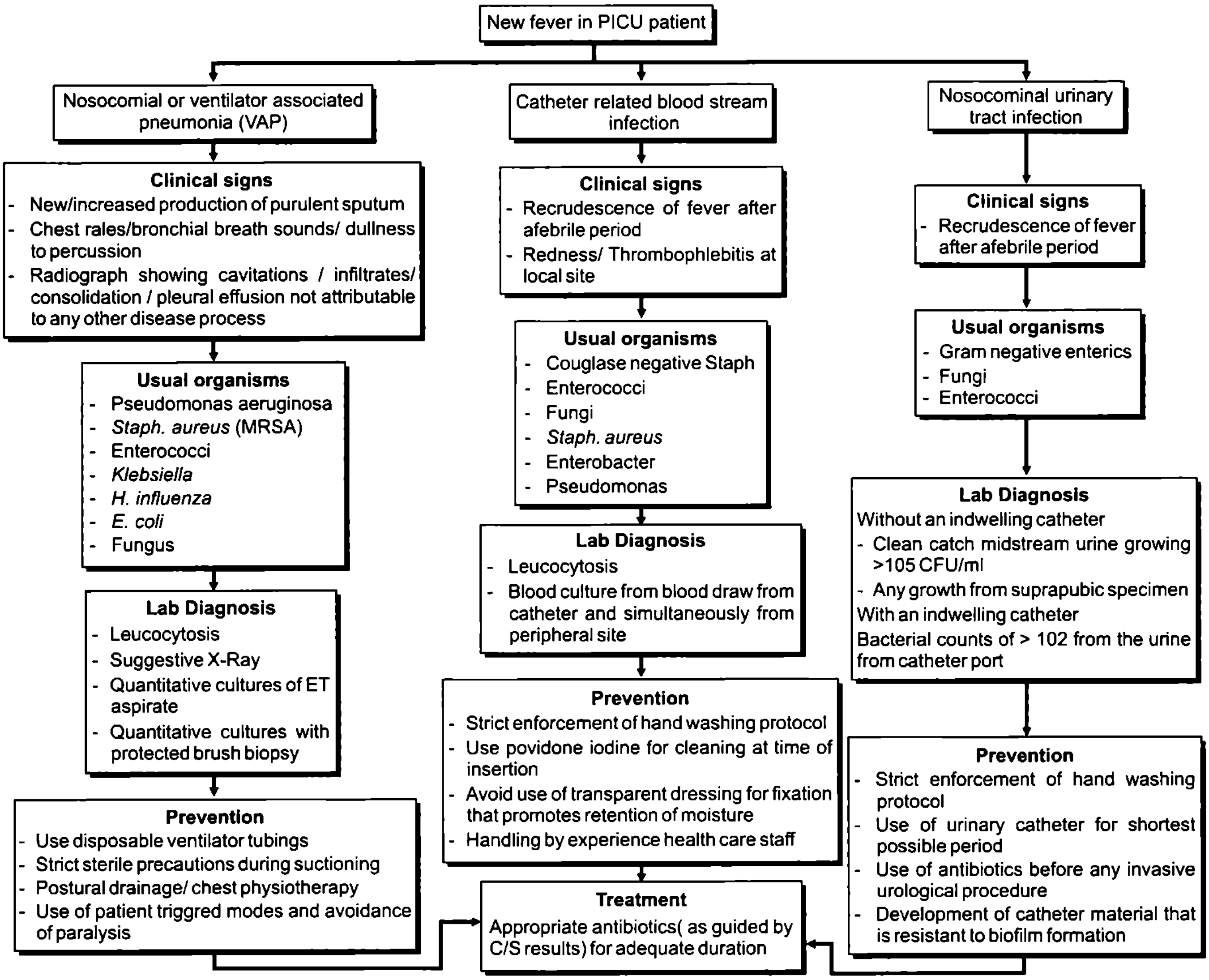
Hand Hygiene

Semmelweiss first observed the value of hand hygiene for the prevention of cross infection. Hand hygiene prevents cross-infection in hospitals, but adherence to guidelines is poor among healthcare workers. Traditional hand washing requires time and commitment. Alcohol based hand-rub solutions requires less time, act faster, irritate less and have been proved to contribute to increased compliance and are associated with a reduced rate of transmission of surface organisms.[33]

The Centres For Disease Control And Prevention have recommended contact precautions for preventing the spread of hospital organisms. Of these measures, hand washing remains the most important tool. However, it alone cannot prevent NI as surface contamination and transmission is also an important factor. Surfaces are considered non-critical items as they come in contact with intact skin. Routine disinfection of floors, walls and other surfaces is therefore considered controversial. However, the risk is when contaminated surfaces and hands or critical equipment come in contact and the bacteria are then carried to the patient who may have a breach in the normal protective barriers of the body. Therefore it seems prudent to clean and disinfect even non-critical surfaces on a regular basis.[34]

Guidelines should be clear and easy to follow for them to become standard of care. It should not be left to the health care worker to decide whether

Flow chart 82.1: New fever in PICU patient


New fever in PICU patient
Nosocomial or ventilator associated pneumonia (VAP)
Catheter related blood stream infection
Nosocominal urinary tract infection
Clinical signs
- New/increased production of purulent sputum
- Chest rales/bronchial breath sounds/ dullness to percussion
- Radiograph showing cavitations / infiltrates/ consolidation / pleural effusion not attributable to any other disease process
Usual organisms
- Pseudomonas aeruginosa
- Staph. aureus (MRSA)
- Enterococci
- Klebsiella
- H. influenza
- E. coli
- Fungus
Lab Diagnosis
- Leucocytosis
- Suggestive X-Ray
- Quantitative cultures of ET aspirate
- Quantitative cultures with protected brush biopsy
Prevention
- Use disposable ventilator tubings
- Strict sterile precautions during suctioning
- Postural drainage/ chest physiotherapy
- Use of patient triggred modes and avoidance of paralysis
Clinical signs
- Recrudescence of fever after afebrile period
- Redness/ Thrombophlebitis at local site
Usual organisms
- Couglase negative Staph
- Enterococci
- Fungi
- Staph. aureus
- Enterobacter
- Pseudomonas
Lab Diagnosis
- Leucocytosis
- Blood culture from blood draw from catheter and simultaneously from peripheral site
Prevention
- Strict enforcement of hand washing protocol
- Use povidone iodine for cleaning at time of insertion
- Avoid use of transparent dressing for fixation that promotes retention of moisture
- Handling by experience health care staff
Treatment
Appropriate antibiotics(as guided by C/S results) for adequate duration
Clinical signs
- Recrudescence of fever after afebrile period
Usual organisms
- Gram negative enterics
- Fungi
- Enterococci
Lab Diagnosis
Without an indwelling catheter
- Clean catch midstream urine growing >105 CFU/ml
- Any growth from suprapubic specimen
With an indwelling catheter
Bacterial counts of > 102 from the urine from catheter port
Prevention
- Strict enforcement of hand washing protocol
- Use of urinary catheter for shortest possible period
- Use of antibiotics before any invasive urological procedure
- Development of catheter material that is resistant to biofilm formation

a particular situation warrants hand washing. The Indian Society of Critical Care Medicine also has clear guidelines that are easy to follow.[35]

The worst possible situation an intensivist faces is one where a child is showing apparent recovery from a serious illness requiring full life support starts showing signs of a possible NI. Usually the antibiotic armamentarium has been exhausted, vascular access is precarious and hence precious, parenteral or enteral feeding is essential and the staff is taking a much-needed breather from minute to minute-critical care (Flow chart 82.1). The longer the patient stays, the more difficult the vascular access, the more the problems of MV, the higher the chances of slipping up in infection control protocols. This, coupled with a debilitated patient adds to the risk of VAP, blood stream infection and catheter associated UTI (CAUTI). (*author's note: In a situation where the team is frustrated with vascular access and emotions are frayed, we call in a skilled member of the adult team to help*).

This is a typical situation where the old clichéd proverb "prevention is better than cure" comes in really handy.

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CHAPTER

83

The Immunocompromised Child in the Pediatric Intensive Care Unit

Amita Mahajan

The commonest etiology for severe immunocompromised status in the current scenario is the child undergoing treatment for cancer. This is followed by children with HIV (Human immunodeficieny virus). Primary immunodeficiencies are rare but these children are extremely vulnerable and may need to be admitted to the pediatric intensive care unit (PICU) especially with fulminant sepsis and septic shock. Children with conditions such as severe aplastic anemia are the other category of patients that one may need to transfer to the PICU, again usually in the setting of infectious complications. As the long-term survival of children with cancer has dramatically improved because of multi-modal treatment strategies; intensive care medicine has become more relevant for these patients. Therefore, it has become necessary for pediatric oncologists, hematologists and pediatric intensivist to work together. Most of the discussion in the current chapter pertains to the child with cancer undergoing treatment and various critical care issues in the medical management of such a child.

In the past there was resistance to admitting these patients to intensive care as outcomes were poor. This scenario has changed dramatically in recent times. Overall there has been a very significant improvement in the survival of oncology patients admitted to the PICU especially for those with either a systemic or serious respiratory infection.[1] A recent study[2] reported a 66 percent 30-day survival rate. Such high rates justify early admission to the PICU of children in whom signs of multi-organ failure begin to develop as reflected by high PRISM scores and the need for ventilatory and inotropic support. The major factor that needs to be considered is that there is no evidence of progressive disease. Organ failure, i.e. cardiovascular failure requiring vasopressors, respiratory failure requiring mechanical ventilation and renal failure requiring hemodialysis, is most significantly associated with poor outcome. A retrospective analysis of cancer patients[3] admitted to the PICU revealed that the commonest indication for admission to the PICU was respiratory insufficiency. Other indications included cardiovascular insufficiency, renal failure, neurologic impairment, ileus and tumor associated complications.

However, there is evidence that these patients have poor outcomes after cardiopulmonary resuscitation. A retrospective study[4] that evaluated the effectiveness of CPR in oncology patients reported that only 2 percent of patients following a cardiopulmonary arrest reached discharge. Patients who survived after CPR and were discharged from the hospital were those who had acute ventricular dysrhythmias and were resuscitated promptly. The authors suggested that cancer patients requiring admission to an ICU should receive full supportive care short of resuscitation. Recent study showed outcomes of patients requiring PICU after bone marrow transplantation was poor, if ventilation was required for longer than 48 hours.[5]

There is often debate among specialists on the risk of therapeutic doggedness and the right to die with dignity. There are no specific tools to guide decision-making prior to transfer to PICU. Due to the very specificity of pediatric oncology, it is difficult to extrapolate from the available adult studies and decisions have to be made on an individual basis.

These patients may need to be sent to a PICU at different steps in their clinical course—at the time of diagnosis, during the curative treatment, or after treatment failure. For each step, there is a need for a wider debate between oncologists, intensivists, nurses, psychologists and the child's family in order to define the most consensual decisions. The development of validated prognostic scores for this particular population will be very helpful for decision-making.[6] As frequently as possible the decision should be anticipated before the transfer of the child to the intensive care unit.

Infectious Complications in the Immunocompromised Child

It is important to recognise that there are variations among patients in the degree to which they are immunocompromised, the type of impairment, and, consequently, the type of infections to which they are susceptible. An understanding of the nature of immune defects, the clinical presentation of common infectious syndromes, the likely pathogens, and the appropriate management of these situations is critically important. The key factors that predispose these children to serious infections are:

- Neutropenia
- Lymphopenia and cellular immune dysfunction
- Loss of integumentry barriers as in severe mucositis
- Presence of catheters in situ such as a PICC line, or portacath, etc.
- Associated malnutrition.

The classical features of infections in the immunocompromised child are:

- *Unusual severity* These children may have serious infections because of opportunistic organisms such as Staph epidermidis. Viral infections such as Respiratory syncitial, influenza etc may cause frank pneumonia in these patients.
- *Unusual pathogens* These children may have infections due to unusual pathogens such as cryptococcus, stenotrophomonas maltophilia.
- *Unusual sites* These patients may manifest with infections at unusual sites such as typhlitis (inflammation of the cecum), or brain abscess.

A number of organisms may be implicated in infectious complications in the immunocompromised child but episodes that may require admission to the PICU are essentially because of:

Gram-negative sepsis due to:

- Enterobacteriaceae (*E. coli*, Klebsiella, Enterobacter, Serratia).
- *Pseudomonas aeruginosa*, Stenotrophomonas maltophilia

Severe respiratory infection due to:

- RSV (Respiratory syncitial virus), Influenza, Parainfluenza.

Invasive Fungal Infection

- Aspergillus, Cryptococcus, Candida.

With earlier use of broad spectrum antibiotics in the patient with febrile neutropenia, septic shock is fortunately less common. However, it is important to remember that severely neutropenic patients may not be able to generate the usual response to an infection in the form of fever. With increasing use of indwelling catheters, the incidence of gram-positive infections has increased and is now responsible for nearly one-half of the infectious episodes. However, these rarely cause septicemic shock. The usual first line antibiotic combinations used in patients with febrile neutropenia are:

Third generation cephalosporins and aminoglycoside or

Piperacillin—Tazobactam with aminoglycoside.

Fourth generation cephalosporins like cefipime, flouroquinolones are other options.

Glycopeptide antibiotics such as Teicoplanin and Vancomycin are added if there are indwelling catheters and/or positive cultures for Staph epidermidis.

Carbapenems form the backbone of second line antibiotic regimes.

Infections in the Central Venous Line

A number of these patients will have central venous access for administration of chemotherapy, etc. Infections of the central venous catheters are notoriously difficult to eradicate and may need removal. This decision, however, should be taken on an individual basis depending on the organism isolated, clinical condition and the need for a secure venous access. It may be possible to salvage lines infected with gram-positive organisms. However, children with gram-negative infections especially from the pseudomonas family may often need line removal.

Prophylaxis for Fungal Infections

All these patients would be on oral anti-fungal prophylaxis anyway because of neutropenia. It is very important to continue this. Persistent neutropenia and treatment with broad spectrum antibiotics are the most important predisposing factors for the development of invasive fungal infections. It is therefore routine policy that severely neutropenic patients who have been on intravenous antibiotics should be commenced on prophylactic antifungal treatment with amphotericin B in a low dose.

Pneumonia in the Immunocompromised Child

See Chapter on Recurrent Chest Infections.

Pulmonary infections in the immunocompromised child can rapidly progress to respiratory failure, and therefore, initial evaluation needs to be performed expeditiously. The extent to which a specific etiology for the pulmonic process is investigated will depend on the clinician's judgement of the immune status of the patient and his or her degree of illness.

Apart from the usual pathogens one needs to consider the possibilities of PCP *(Pneumocystis carinii* viral pneumonitis) CMV (Cytomegalo virus), RSV, Influenza, Parainfluenza and invasive fungal infections in these children.

The initial evaluation of the child with pneumonia should include a chest radiograph, blood cultures, hematologic indices, pulse oximeter reading (or arterial blood gases in more critical situations), and collection and examination of available material. Sputum is usually not available in granulocytopenic patients. Nasopharyngeal aspirates, particularly for viral pathogens, including respiratory syncytial virus, parainfluenza and adenovirus may be useful.

Further radiographic evaluation with a CT scan may provide information regarding the pattern and extent of disease that may not be evident on plain film alone. It is important to remember, however, that the radiographic presentation may be extremely variable for any given etiology and the differential diagnosis of most radiographic findings remains broad.

Flexible bronchoscopy can provide evidence for a specific diagnosis in immunocompromized patients with pneumonia. The yield of bronchoscopy depends on the clinical situation and the extent of prior therapy. Bronchoalveolar lavage can yield the diagnosis in approximately 80 percent of *Pneumocystis carinii* pneumonia, whereas, it significantly less sensitive for fungal infections or bacterial infections in patients who have received prior therapy. Transbronchial biopsy may increase the diagnostic yield in some patients; however, this procedure is limited in the very small children by the size of the equipment required.

Pneumocystis carinii pneumonia is pathognomonic of immunedeficiency. Patients usually present with cough, tachypnea and hypoxemia. Fortunately this is rare as most patients are on PCP prophylaxis. Clinical signs are usually subtle. Chest radiographs may show the classical picture of bilateral perihilar shadows and interstitial infiltrates. Treatment is with high dose septran. Patients may need ventilatory support.

It is important to realize that the immunocompromized child does not tolerate ventilation well. These children are prone to have much more significant ventilator induced lung injury than the immunocompetent child. Therefore, wherever possible, invasive ventilation should be avoided. Continuous positive airway pressure or noninvasive ventilation may often help to stabilize these patients.

Cardiothoracic Emergencies

The commonest cardiothoracic emergency is the occurrence of superior vena cava syndrome and superior mediastinal syndrome. The commonest oncological condition presenting in such a way is T-cell non-Hodgkin's lymphoma or leukemia. There is usually a large anterior mediastinal mass compressing both the SVC and trachea. Pleural and pericardial effusions may co-exist and contribute further to cardio-respiratory compromise. Starting treatment promptly is of utmost importance.[7] Usually these tumors are very responsive to steroid therapy. If there is frank or imminent airway compromise, a small radiation dose to the anterior mediastinum may avoid frank decompensation.

If ventilation is required in such a situation, it is important to recognize that it may be much easier to ventilate the patient in a prone or lateral position so as to push the mediastinal mass away from the airway.

Occasionally very large pleural effusions may themselves cause severe respiratory compromise. Pleurocentesis can only provide transient relief as these effusions rapidly reaccumulate. Again initiating definitive treatment is a matter of urgency. Procedures like pleurodesis are rarely indicated as most patients respond very well to treatment.

Shock

Shock occurs when cardiovascular dysfunction results in inadequate perfusion of vital organs. Shock is relatively common in children with cancer. The etiologic classification is identical as in any other child but the likely etiologies are different than in the immunocompetent child.

Hypovolemic Shock

- Sepsis
- Hemmorage: Bladder (drugs, adenovirus)
  - Intestine (Typhlitis, *C. difficile*)
  - Massive hemoptysis (Aspergillus, Tumor invasion)
  - Intractable emesis
- Pancreatitis (L-asparaginase, glucocorticoids)
- Addisonian crisis
- Diabetes Mellitus (After glucocorticoids)

Distributive Shock

- Anaphylaxis commonly due to L-asparaginase, Carboplatin, Etoposide, Amphotericin B.
- Sepsis
- Veno-occlusive disease

Cardiogenic Shock

- Treatment related: Anthracyclines, cyclophosphamide, radiotherapy
- Cardiac tamponade
- Myocarditis
- Metabolic.

Hematological Complications

Disseminated Intravascular Coagulation (DIC)

It is usually seen in the setting of fulminant septicemia. It may also be seen at presentation in patients with AML M3 or Acute Promyelocytic Leukemia. The management of DIC is as in any other situation with platelets, fresh frozen plasma and effective management of the infection.

Bleeding

Till blood component therapy was easily available, the commonest reason for these children to die was bleeding with the risk of intracranial bleed being very high. With the availability of platelet concentrates and single donor platelets, it should be possible to prevent these complications. It is generally recommended to maintain platelets above 10,000/cu mm at all times and above 20,000 in patients with fever or sepsis. Actively bleeding patient and a documented rapid fall of platelet count are two important indications for platelet transfusion.

Hyperleucocytosis Patients with very high leucocyte counts at presentations are at risk of serious pulmonary and neurological complications because of vascular stasis. Clinically this usually becomes significant when the white cell count is in excess of 200,000/cu mm. Hyperleucostasis can cause death by CNS hemorrage or thrombosis, pulmonary leucostasis, and the metabolic derangements that accompany tumor lysis. Treatment is to maintain hydration and initiate treatment in a staggered way to reduce the chances of tumor lysis syndrome (TLS). Leukaphresis reduces the incidence of TLS and may reduce the incidence of complications.

Neurologic Complications

Infections

It is important to consider the possibility of CNS infections in the immunocompromized child with obvious and often subtle neurological findings. Apart from the usual pathogens, one needs to consider pathogens such as cryptococcus, cytomegalovirus, citrobacter, aceinatobacter, etc. The presentation may also be unusual in the form of intracranial abscesses, or encephalitis.

Seizures

A seizure is a symptom of an underlying pathological process. The investigative work up of seizures is same as that in any other case. The main differentials would be:

a. *Tumor:* Primary CNS tumor, Metastatic disease, Leukemic meningitis, Hyperleucocytosis.
b. *CNS Infection:* Viral, Bacterial, Fungal, protozoal
c. Cerebrovascular accident
d. Metabolic abnormality

Metabolic Complications

Again there could be many reasons for metabolic derangements but certain conditions are unique to these children such as *Acute Tumor Lysis Syndrome (ATLS)*. Classically this is a triad of hyperuricemia, hyperkalemia, and hyperphosphatemia. There may be associated hypocalcemia because of calcium phosphate formation. It usually occurs in tumors that have a very high growth fraction and are extremely sensitive to therapy. The tumor cells undergo rapid lysis releasing the nuclear and cellular degradation products which are responsible for the pathophysiology. Patients may present with ATLS at the time of diagnosis but usually occurs within 12 to 48 hrs after initiating therapy.

Care in the PICU

The majority of these children will be admitted to the PICU with infectious complications. However, it is very important to protect them from further hospital acquired infections. Ideally, these patients should have reverse isolation. This may however not be possible in the intensive care setting. One cannot over emphasize the importance of rigorous hand washing prior to handling these patients each time. Also any equipment that is used should be cleaned prior to usage. If possible, one should avoid sharing of equipment.

A number of these patients will have central lines in situ and again care needs to be taken whilst handling them.

In summary, the outcome of these children has improved dramatically in recent times. Treatment modalities today are more intense and can lead to a number of complications that may mandate intensive care for these children. Pediatric Oncologists and Hematologists are willing to accept these toxicities as long as we can support these children through these. It is therefore, very important for all specialists involved in the care of these children as a team.

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CHAPTER

Pediatric HIV Infections

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AIDS

Definition

Clinical syndrome resulting from infection by HIV type I which preferentially infects and destroys CD_4 helper/ inducer T cells. This leads to a severe immuno-deficiency involving both cell mediated and humoral immunity and makes the patient highly susceptible to life threatening bacterial and opportunistic infections and to certain tumors.

Most HIV infection among children is acquired perinatally and most perinatal transmission occurs during or near the time of birth, which raises the possibility of initiating treatment in an infected infant during the period of initial(primary) HIV infection. Perinatal HIV infection occurs during the development of the infant's immune system; thus both the clinical manifestations of HIV infection and the course of immunological and virological markers of infection differ from those of adults.

Identification of Perinatal HIV Exposure

Appropriate treatment of infants with HIV infection requires HIV-exposed infants to be identified as soon as possible after birth, which can be accomplished through the identification of women with HIV infection before or during pregnancy. Universal HIV counseling and voluntary HIV testing with consent are recommended as standard of care for all pregnant women. Early identification of women with HIV infection is crucial for the health of such women and for care of HIV exposed and infected children. Knowledge of maternal HIV infection during the antenatal period enable HIV-infected women to receive appropriate antiretroviral therapy and prophylaxis against opportunistic infections for their own health. Provision of antiretroviral chemotherapy with ZDV(Zidovudine) during pregnancy and labor, and their newborn to reduce the risk for HIV transmission from mother to child. Counseling of infected women about the risks of transmission through breast milk and advising against breast feeding in the United States and other countries where safer alternatives to breast milk are available.

Diagnosis of HIV Infection in Infants (Flow chart 84.1)

HIV infection can be diagnosed definitively in most infected infants by age 1 month and in virtually all infected infants by age 6 months using viral diagnostic assays.

A positive virological test result (i.e. detection of HIV by culture, DNA or RNA polymerase chain reaction[PCR]) indicates possible HIV infection and should be confirmed by a repeat virological test on a second specimen as soon as possible.

Diagnostic testing should be performed before the infant is 48 hours of age, at 1 to 2 months and 3 to 6 months. Testing at age 14 days may also be advantageous for early detection of infection.

HIV DNA PCR is the preferred virologic method for diagnosing HIV infection during infancy.

Assays that detect HIV RNA in plasma also may be useful for diagnosis of perinatal infection. HIV culture has sensitivity similar to that of DNA PCR for diagnosis of infection. However HIV culture is more complex and expensive to perform than is DNA

PCR and definitive results may not be available for 2 to 4 weeks. Although use of standard and immune-complex dissociated p-24 antigens tests are specific for HIV infection and have been used to diagnose infection in children, the sensitivity is less than that of other virologic tests.

Initial testing is recommended by 48 hours because nearly 40 percent of infected infants can be identified by this time.

Blood samples from the umbilical cord should not be used for diagnostic evaluation.

Repeat diagnostic evaluation can also be considered at age 14 days in infants with negative tests at birth, because the diagnostic sensitivity of virologic assays increases rapidly by age 2 weeks and early identification of infection would permit modification of antiretroviral therapy from the standard 6 week course of neonatal ZDV chemoprophylaxis to more aggressive combination antiretroviral therapy.

Infants with initially negative virologic results should be retested at 1 to 2 months .With increasing use of ZDV to reduce perinatal transmission, most HIV exposed neonates will receive 6 weeks of antiretroviral chemoprophylaxis. Although antiretroviral chemoprophylaxis could theoretically affect the predictive value of HIV virologic testing , ZDV monotherapy does not delay the detection of HIV by culture in infants and does not decrease the sensitivity and predictive value of many virologic assays.

HIV exposed children with repeated negative virologic assays at birth and at age 1 to 2 months should be retested at 3 to 6 months of age.

HIV infection is diagnosed by two positive HIV virologic test results from separate blood samples.

HIV infection can be reasonably excluded among children with 2 or more negative results, two performed at age ≥ 1 month and one performed at age ≥ 4 months.

Two or more negative HIV IgG antibody test results obtained at age >6 months with an interval of at least 1 month between tests also can be used to reasonably exclude HIV infection in children with no clinical evidence of HIV infection.

HIV infection can be excluded definitively if HIV IgG antibody is negative in the absence of hypo-gamma-globulinemia at age 18 months and if the child has both no clinical symptoms of HIV infection and negative HIV virologic assays.

MONITORING PEDIATRIC HIV INFECTION

Immunologic Parameters in Children

Clinicians interpreting CD4+ T -lymphocyte number in children must consider age as a variable.CD4+ T -lymphocyte count and percentage values in healthy infants who are not infected with HIV are considerably higher than those observed in uninfected adults and slowly decline to adult values by age 6. A pediatric clinical and immunologic staging system for HIV infection has been developed that includes age-related definitions of immune suppression (Tables 84.1 and 84.2). Although the CD4+ absolute number that identifies a specific level of immune suppression changes with age, the CD4+ percentage that defines each immunologic category does not. Thus, a change in CD4+ percentage, not number, may be a better marker to identify disease progression in children. In infected children and adults, CD4+ cell count declines as HIV infection progresses, and patients with lower CD4+ cell counts have a poorer prognosis than do patients with higher counts. Because knowledge of immune status (i.e., CD4+ T -lymphocyte count and percentage) is essential when caring for HIV - infected infants and children, **CD4+ T -lymphocyte values should be obtained as soon as possible after a child has a positive virologic test for HIV and every 3 months thereafter.**

The CD4+ T -lymphocyte count or percentage value is used in conjunction with other measurements to guide antiretroviral treatment decisions and primary prophylaxis of pneumocystis carinii pneumonia (PCP) after 1 year of age.

HIV RNA in Children

Viral burden in peripheral blood can be determined. Despite data indicating that high RNA levels are associated with disease progression, the predictive value of specific HIV RNA levels for disease progression and death for an individual child is only moderate. HIV RNA levels may be difficult to interpret during the first year of life, because levels are high and there is marked overlap in levels between children who have rapid disease progression and those who do not. Additional data indicate that **CD4+ T -lymphocyte percentage and HIV RNA copy number** at baseline and changes in these parameters overtime contribute to prediction

Flow chart 84.1

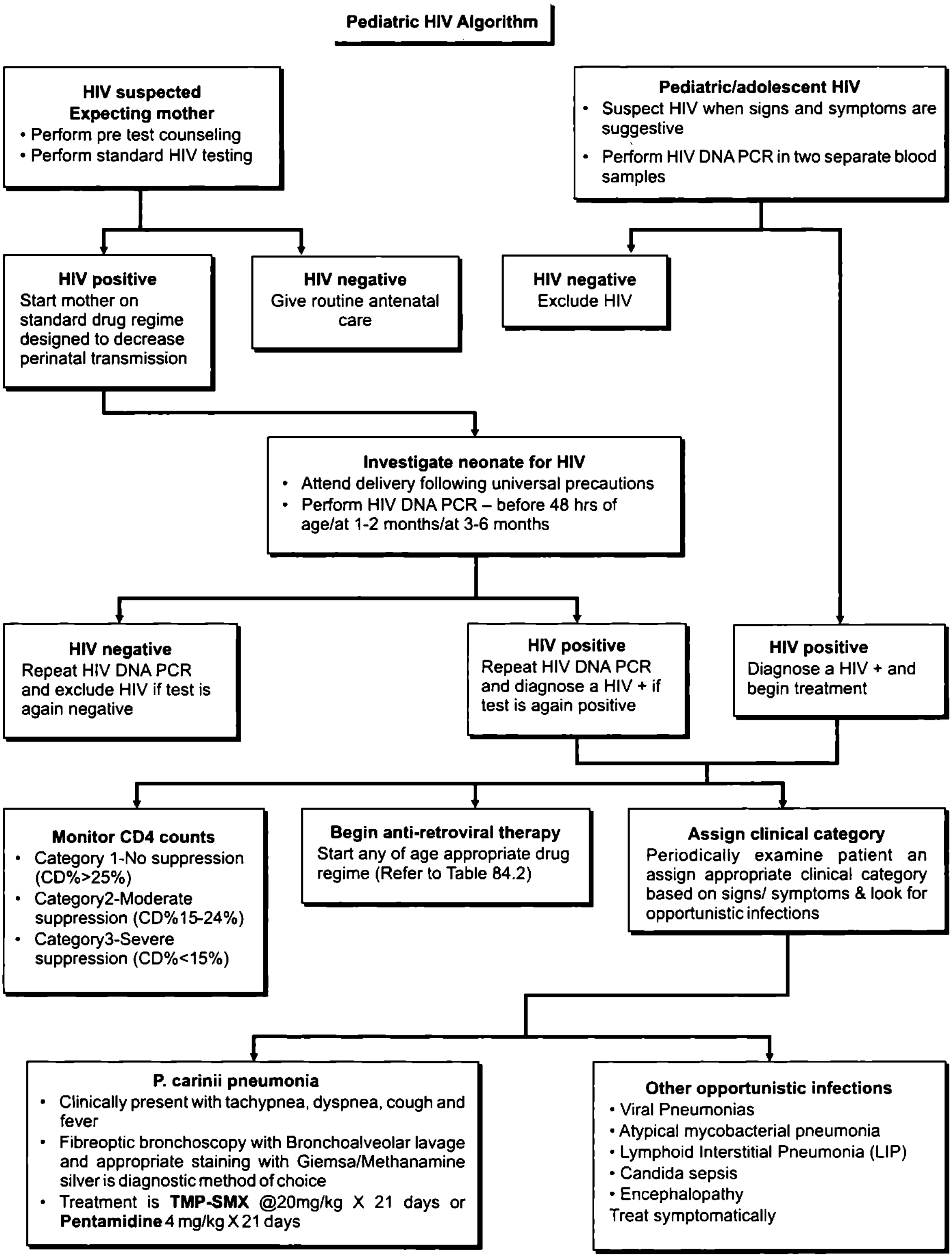

Pediatric HIV Algorithm
HIV suspected
Expecting mother
• Perform pre test counseling
• Perform standard HIV testing
Pediatric/adolescent HIV
• Suspect HIV when signs and symptoms are suggestive
• Perform HIV DNA PCR in two separate blood samples
HIV positive
Start mother on standard drug regime designed to decrease perinatal transmission
HIV negative
Give routine antenatal care
HIV negative
Exclude HIV
Investigate neonate for HIV
• Attend delivery following universal precautions
• Perform HIV DNA PCR – before 48 hrs of age/at 1-2 months/at 3-6 months
HIV negative
Repeat HIV DNA PCR and exclude HIV if test is again negative
HIV positive
Repeat HIV DNA PCR and diagnose a HIV + if test is again positive
HIV positive
Diagnose a HIV + and begin treatment
Monitor CD4 counts
• Category 1-No suppression (CD%>25%)
• Category2-Moderate suppression (CD%15-24%)
• Category3-Severe suppression (CD%<15%)
Begin anti-retroviral therapy
Start any of age appropriate drug regime (Refer to Table 84.2)
Assign clinical category
Periodically examine patient an assign appropriate clinical category based on signs/ symptoms & look for opportunistic infections
P. carinii pneumonia
• Clinically present with tachypnea, dyspnea, cough and fever
• Fibreoptic bronchoscopy with Bronchoalveolar lavage and appropriate staining with Giemsa/Methanamine silver is diagnostic method of choice
• Treatment is TMP-SMX @20mg/kg X 21 days or Pentamidine 4 mg/kg X 21 days
Other opportunistic infections
• Viral Pneumonias
• Atypical mycobacterial pneumonia
• Lymphoid Interstitial Pneumonia (LIP)
• Candida sepsis
• Encephalopathy
Treat symptomatically

Table 84.1: 1994 Revised Pediatric HIV Classification System: Immunologic categories based on age-specific CD4+ lymphocyte count and percentage

	Age of Child					
Immune Category	*<12 mo*		*1-5y*		*6-12 y*	
	Number /μ L	*(%)*	*Number /μ L*	*(%)*	*Number /μ L*	*(%)*
Category 1: no suppression	≥"1500	(≥"25)	≥"1000	(≥"25)	≥"500	(≥"25)
Category 2: moderate suppression	750-1499	(15-24)	500—999	(15-24)	200-499	(15-24)
Category 3: severe suppression	<750	(<15)	<500	(<15)	<200	(<15)

Modified from Centers for Disease Control. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR. 1994; 43(No. RR-12): 1-10.

Table 84.2: 1994 Revised HIV pediatric classification system

Clinical Categories	
Category N : Not symptomatic	Children who have signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in Category A
Category A: Mildly Symptomatic	Children with two or more of the conditions listed below but none of the conditions listed in categories B and C.
	Lymphadenopathy (≥0.5 cm at more than two sites; bilateral =one site)
	Hepatomegaly
	Splenomegaly
	Dermatitis
	Parotitis
	Recurrent or persistent upper respiratory infection, sinusitis or otitis media
Category B: Moderately Symptomatic	Children who have symptomatic conditions other than those listed for category A or C that are attributed to HIV infection. Examples of conditions in clinical category B include but are not limited to:
	Anemia (<8 gm/dL), neutropenia (<1000/mm3) or thrombocytopenia (<100 000/mm^3) persisting ≥" 30 days
	Bacterial meningitis, pneumonia, or sepsis (single episode)
	Candidiasis, oropharyngeal (thrush) persisting (>2 months) in children >6 m
	Cardiomyopathy, Cytomegalovirus infection, with onset before 1 month of age
	Diarrhea, recurrent or chronic
	Hepatitis, HSV stomatitis, recurrent (more than two episodes within 1 year)
	HSV bronchitis, pneumonitis, or esophagitis with onset before 1 month of age
	Herpes zoster (shingles) involving at least two distinct episodes or more than one dermatome
	Leiomyosarcoma. LIP or pulmonary lymphoid hyperplasia complex
	Nephropathy, Nocardiosis
	Persistent fever (lasting > 1 month)
	Toxoplasmosis, onset before 1 month of age
	Varicella, disseminated (complicated chickenpox)
Category C: Severely Symptomatic	Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of LIP (which is a category B condition)
	Serious bacterial infections, multiple or recurrent (i.e. any combination of at least two culture-confirmed infections within a 2-year period) of the following types: Septicaemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and in-dwelling catheter-related infections)
	Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)

Contd...

Contd...

Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
Cryptococcosis, extrapulmonary Cryptosporidiosis or isosporiasis with diarrhea persisting >1 month
Cytomegalovirus disease with onset of symptoms at age > 1 month (at a site other than liver; spleen, or lymph nodes)
Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings:1)failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; 2) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements or brain atrophx demonstrated by CT or MRI (serial imaging is required for children <2 years of age); 3) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
HSV infection causing a mucocutaneous ulcer that persists for > 1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child > 1 month of age
Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
Kaposi's sarcoma
Lymphoma, primary, in brain
Lymphoma, small, noncleaved cell (Burkitt's), or immunoblastic or large cell lymphoma of B-cell or unknown immunologic

Modified from Centers for Disease Control. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR. 1994;43(No. RR-12):1-10.

of mortality risk in infected children, and the use of the **two markers together may define prognosis more accurately.**

Specific issues in antiretroviral therapy for HIV-infected adolescents

Adult guidelines for antiretroviral therapy are appropriate for postpubertal adolescents who were infected sexually or via intravenous drug use during adolescence because such HIV -infected adolescents follow a clinical course that is more similar to that in adults than to that in children. Most adolescents have been infected during their teen-age years and are in an early stage of infection, making them ideal candidates for early intervention. A limited but increasing number of adolescents with HIV infection are long-term survivors of HIV infection acquired perinatally or via blood products as young children. Such adolescents may have a unique clinical course that differs from adolescents infected later in life.

Opportunistic infections and other clinical manifestations of HIV disease in children.

Pneumocystis Carinii Pneumonia (PCP)

PCP is a hallmark opportunistic infection of pediatrics AIDS epidemic known as "AIDS pneumonia" This opportunistic infection is the most common AIDS defining illness in children. PCP is an infection of early infancy and most children are affected at between 4 and 6 months of age. The risk of PCP in the first year of life for perinatally infected children not receiving prophylaxis is estimated to be approximately 12 percent.The revised guidelines recommend prophylaxis for all HIV infected infants, independent of CD4 count and HIV infection status starting at 4 to 6 weeks of life until 4 months of age, when a more definite diagnosis of HIV infection can be made using polymerase chain reaction(PCR).[5]

Pathogenesis of Pneumocystis Carinii Infection

P. Carinii thought to be protozoan is now believed to be more closely related to fungi. *P. Carinii* is not easily cultured, making diagnosis dependent on the demonstration of organisms in tissues or secretions. *P. Carinii* establishes infection within the alveoli, where it proliferates as an extracellular parasite.

Clinical and Radiological Presentation of PCP

Children with PCP present with a tetrad of radiological findings; tachypnea, dyspnea, cough and fever. Physical examination findings include tachycardia and respiratory distress, accelerating tachypnea and diffuse retractions. Pulmonary auscultation is typically non specific. PCP is characterised by rapidly progressive hypoxemia.

Early radiographic findings may be normal or can include hyperinflation with peribronchial thickening. As the disease progresses,the chest radiographic findings typically evolve to reveal bilateral alveolar or interstital infiltrates usually spreading peripherally from the perihilar region to involve both lung fields. Further progression results in coalescent bilateral airspace disease with air bronchogram. Less typical radiographic findings include focal or patchy infiltrates, cavities or effusions.

Diagnosis: A confirmed diagnosis has implications for the measurement of treatment efficacy and decisions regarding secondary prophylaxis.

Fibreoptic bronchoscopy with bronchoalveolar lavage has been shown to be a safe and sensitive method for the diagnosis of PCP.

Other diagnostic methods include sputum, tracheal wash for intubated children and open lung biopsy. Open lungbiopsy is now typically reserved for children with inconclusive results from less invasive procedures and worsening clinical status despite treatment.

The wright-geimsa procedure stains trophozoite and intracystic sporozoite forms of *P. Carinii* and is commonly used as rapid screening test. The Papanicolaou stain which identifies the alveolar exudates of PCP rather than the organism can be used for screening. The Methenamine silver stain and direct immuno- flouroscent staining with monoclonal antibody detect cyst forms of the organism and can be used for the confirmation of screening results.

Treatment and Prognosis for children with Pneumocystis carinii:

Therapy for PCP should include treatment with trimethoprim-sulphamethoxazole (TMP-SMX) or pentamidine, intravenous steroids and intensive respiratory support.TMP-SMX is the treatment of choice for children with PCP. The dose is 20 mg/kg divided into 4 daily doses for 21 days. Medication can be changed to a oral formulation when clinical improvement is sustained. Pentamidine 4 mg/kg given as a single dose for 21 days is generally reserved for children who cannot tolerate TMP-SMX secondary to adverse effects and for those who fail therapy.

Comprehensive respiratory support, including supplemental oxygen, ventilatory support and good pulmonary toilet is essential to ensure a satisfactory outcome for patients with this disease. Children are at risk for respiratory distress syndrome and secondary complications including pneumothorax. Secondary bacterial complications may also complicate the course of disease.

Other common infections seen in HIV patients are:

Viral pneumonia(various viruses including CMV)

Atypical mycobacterial pneumonia lymphoid interstitial pneumonitis(LIP), Candida sepsis, septic shock and multiorgan failure.

Encephalopathy may be an important feature of central nervous system involvement.

All infections need to be treated symptomatically.

Currently Available Antiretroviral Agents (Table 84.3)

Two classes of drugs target the reverse transcriptase enzyme-

Nucleoside reverse transcriptase inhibitors (NRTIs)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs), while a third class, the protease inhibitors, target the viral protease.

Although some drugs have been approved for the pediatric age group, identifying the optimal dosing regimen may still be an ongoing process. The recommended dosing schedules listed in Table 3 are specific to pediatric populations. For infants less than 2 years of age and especially for newborns, specialized dosing schedules may be necessary and are still in the process of evaluation for many of the newer antiretroviral agents. In addition, transition from childhood to adolescence to adulthood regarding recommended dosing may not be smooth or uniform, and caution must be exercised when approaching these transition periods.

General Features of Antiretroviral Agents

Nucleoside Reverse Transcriptase Inhibitors(NRTIs)

Zidovudine (ZDV) was the first of the NRTIs and the first antiretroviral approved by the FDA for use by children and adults. Additional NRTIs soon became available in the form of didanosine and zalcitabine. These three agents formed the mainstay of therapy in the late 1980s and early 1990s. ZDV and zalcitabine have relatively short serum half-lives and have routinely been administered every 6 to 8 hours. All antiretroviral agents have documented side effects, and the NRTIs are no exception. Hematologic toxicity in the form of anemia and neutropenia is most common with ZDV; often requiring dose reduction or holidays.

Severe side effects of Didanosine include peripheral neuropathy and pancreatitis. Didanosine is an uncommonly used drug in the pediatric population, with no liquid formulation and a disturbing incidence of painful peripheral neuropathy.

HIV Counselling

Having to deal with infants and children of all ages, pediatricians are used to counsel parents regarding health protection and promotional practices such as immunization and feeding and hence make good counselors.

A pediatrician in addition , faces unique situations, where pre-test and post-test counseling has to be dealt with, not only for positive patients but also for their parents who also need to be tested. A pediatrician thus has to muster all his experience in counseling parents and caregivers of HIV infected baby and plan their future management as well as provide the required psychosocial support system.

Pre and Post Test Counseling

The National AIDS Policy discourages the use of mandatory testing under any circumstances, except for blood and organ donation. Voluntary, Confidential Counseling and Testing (VCCT) is the backbone

Table 84.3: Antiretroviral agents

Generic	Abbreviation	Trade name	Pediatric dosage
Nucleoside reverse transcriptor inhibitors (NRTIs)			
Zidovudine	AZT, ZDV	Retrovir	90-180 mg/m^2 every 6-8 h*α
Didanosine	ddl	Videx	90-150 mg/m2 every 12 h*α
Lamivudine	3TC	Epivir	4 mg/kg bid*α
Stavudine	d4T	Zerit	1 mg/kg ql2h (to 30 kg) *β
Abacavir	ABC	Ziagen	8 mg/kg ql2h *α
Zalcitabine	ddC	Hivid	0.005-0.01 mg/kg q8h*α
Adefovirll	ADV	Preveon	Pediatric dose not established
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Nevirapine	NVP	Viramune	120-200 mg/m2 every 12 h*α
Efavirenz	EFV	Sustiva	200-600 mg qd (by weight) β
Delavirdine	DLV	Rescriptor	Adolescent/ adult = 400 mg tid α
Protease inhibitors			
Ritonavir	RTV	Norvir	400—450 mg/m2 every 12 h*
Nelfinavir	NFV	Viracept	30 mg/kg every 8 h; 55 mg/kg bid*α
Indinavir	IDV	Crixivan	500 mg/m^2 every 8 h β
Saquinavir	SQV	Invirase, Fortovase	50 mg/kg tid [under study
Amprenavir	VX478	Agenerase	20 mg/kg bid *β

**Available in oral solution formulation.*
αAvailable in tablets.
βAvailable in capsules.
bid = twice a day, qd = once a day, tid = three times a day.

of the National AIDS Control Programme. The services for the counseling and testing by ELISA are widely available throughout the country.

Pre Test Counseling

Counseling before testing requires information to be provided on the link between high risk behavior and HIV infection, technical aspects of screening and any possible personal, medical, social, psychological and legal implications of being found either positive or negative. This information is to be provided in a manner that is easy to understand. The potential benefits of voluntary testing should be clearly spelt out as improved health care through nutritional advice, earlier access to care and treatment and prevention of HIV related illnesses. While counseling for testing, the individuals right to undergo the test or to refuse the test should be actively discussed. The individual should feel assured about the confidentiality of the result.

Post Test Counseling

Negative Test

An individual with negative results may feel relieved and euphoric. However he needs to be told about the concept of window period, wherein even an infected individual may have negative test results. If less than six months have elapsed after the last exposure, a repeat test is advised. If he cannot bear the uncertainty for such a long time, he may be advised to take RTPCR and P24 Antigen Detection Test. One can be sure of a negative if more than six months have passed after the last exposure. However if a person indulges in High risk behavior, he should be advised about behavior modification.

Equivocal Test

The meaning of an equivocal test should be explained to the client and he should be advised to undertake another test after 3 months. While awaiting the test results the client should be given information on prevention and offered support.

Positive Test

The HIV infection has various medical, social, emotional and behavioral consequences. Apart from medical problems, the social impact of HIV on interpersonal relationships, marriage and career is profound. The infected person and his family have to cope with feelings of guilt, helplessness or a sense of betrayal. In addition to the emotional turmoil, the infected person has to plan for the future well being of his dependents.Therefore it is necessary for the infected person to be counseled regarding various aspects of HIV infection such that he develops the necessary coping skills.

Counseling individuals who have tested positive must be held in private to ensure confidentiality. The client should be given adequate time to absorb this information. After the initial period of preliminary adjustments, the client should be given clear and factual information of what this news means. This is not the time to speculate about prognosis or about time left to live, but an occasion for providing support and exploring the possibility of achieving solutions to personal and practical problems. If resources are available, treatment options can be discussed and ways of preventing infection to sexual partners and prevention of sharing needles should be discussed.

Counseling the Mother of an HIV Infected Baby

When counseling the mother of an HIV exposed infant, the pediatrician should take into account that the diagnosis may be recent for the mother, whose infection may have been identified during or after pregnancy. If the mother is not already receiving care, she should be referred for HIV care for herself. Some families may require additional support because of HIV illness or death in other family members. Other social factors that may lead to on increased need for social services are poverty, substance abuse, domestic violence and fear of loss of existing supports and services. Pregnant adolescents are particularly vulnerable in this regard.

When counseling parents or caregivers of an HIV exposed infant, the pediatrician should provide an outline of plans of medical care. Important topics to be covered are medications to prevent perinatal acquisition of HIV infection and opportunistic infections, as well as the schedule of follow- up visits for assessment and lab assays. Mothers should be advised not to breastfeed. Parents should be told about the need for prompt assessment if the infant becomes ill. For the infant in foster care, caregivers should have sufficient information about the infants health, including HIV status, to ensure appropriate health care. The necessity of maintaining confidentiality should be emphasized. HIV infection is not a reason for exclusion from health care. Pediatricians should discuss the need for planning for future care if the mother were to become ill with her HIV infection.

FURTHER READING

1. Centers for Disease Control and Prevention. 1995 revised guidelines for prophylaxis against Pneumocystis carnii pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. MMWR. 1995;44(RR-4):1-11.
2. Centers for Disease Control and Prevention. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. MMWR. 1994;43(RR-12):1-10.
3. Centers for Disease Control and Prevention. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome:MMWR CDC surveillance sum 36(suppl):1-15,1987.
4. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. N Engl I Med. 1994; 331 :1173-1180.
5. Singh Surjit, Human immune deficiency virus infection. Indian Pediatr 2000;37:1328-1340.
6. WHO IAP HIV Manual 2005
7. Working Group on Antiretroviral Therapy: National Pediatric HIV Resource Center. Antiretroviral therapy and medical management of the human immunodeficiency virus-infected child. Pediatr Infect Dis J.1993;12:513-522.

APPENDIX
Characteristics of Available Antiretroviral Drugs

NUCLEOSIDE/NUCLEOTIDE ANALOGUE REVERSE TRANSCRIPTASE INHIBITORS (NRTIS/NNRTIS)*†

Abacavir (GW 1592U89, ABC, Ziagen™)

- *URL:* Link to Pediatric Antiretroviral Drug Information
- *Preparations:* Pediatric oral solution:
  - 20 mg/mL
  - Tablets: 300 mg
- *Tablets in combination with zidovudine and lamivudine:*
  - TRIZIVIR-300 mg zidovudine,
  - 150 mg lamivudine,
  - 300 mg abacavir.

Dosage

Neonatal/Infant dose: Not approved for infants less than three months of age. In infants between one and three months of age, a dose of 8 mg/kg of body weight twice daily is under study.

Pediatric/Adolescent dose: 8 mg/kg of body weight twice daily, maximum dose 300 mg twice daily.

Adult dose: 300 mg twice daily.

Adult dose of TRIZIVIR: 1 tablet twice daily.

Major Toxicities

More common: Nausea, vomiting, fever, headache, diarrhea, rash and anorexia.

Less common (more severe): Approximately 5 percent of adults and children receiving ABC develop a potentially fatal hypersensitivity reaction. Symptoms include fever, fatigue, malaise, nausea, vomiting, diarrhea, and abdominal pain or respiratory symptoms such as shortness of breath. Physical findings include lymphadenopathy, ulceration of mucous membranes, and maculopapular or urticarial skin rash. The hypersensitivity reaction can occur without a rash. Laboratory abnormalities include elevated liver function tests, elevated creatine phosphokinase, elevated creatinine and lymphopenia. This reaction generally occurs in the first six weeks of therapy. Patients suspected of having a hypersensitivity reaction should have ABC stopped and not restarted since hypotension and death have occurred upon rechallenge. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Rare: Pancreatitis, increased liver enzymes, elevated blood glucose, elevated triglycerides and fatigue.

Drug Interactions

- No significant interactions between ABC, ZDV, and 3TC.
- ABC does not inhibit, nor is it metabolized by, hepatic cytochrome P450 enzymes. Thus, it should not cause changes in drug levels or clearance of agents metabolized through these pathways, such as PIs and NNRTIs.
- Ethanol decreases elimination of ABC, resulting in a modest increase in drug exposure.

Special Instructions

- Can be given without regard to food.
- Patients and parents must be cautioned about the risk of serious hypersensitivity reaction. A medication guide and warning card should be provided. Patients experiencing a hypersensitivity reaction should be reported to the Abacavir Hypersensitivity Registry (1-800-270-0425).
- Patients should not interrupt therapy without consulting with their physician.

Didanosine (Dideoxyinosine, ddI, Videx®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Pediatric powder for oral solution (when reconstituted as solution containing antacid): 10 mg/mL;

- Chewable tablets with buffers: 25, 50, 100, 150 mg, and 200 mg;
- Buffered powder for oral solution: 100, 167, and 250 mg;
- Delayed-release capsules (enteric-coated beadlets): VIDEX EC- 125, 200, 250 and 400 mg.

Dosage

Neonatal/Infant dose (infants aged < 90 days): 50 mg per m^2 of body surface area every 12 hours.

Pediatric usual dose: In combination with other antiretrovirals: 120 mg per m^2 of body surface area every 12 hours.

Pediatric dosage range: 90 to 150 mg per m^2 of body surface area every 12 hours (Note: may need higher dose in patients with central nervous system disease.)

Adolescent/Adult dose: Body weight $\geq$ 60 kg: 200 mg twice daily. Body weight < 60 kg: 125 mg twice daily. May be administered once daily in adolescents/adults to improve compliance, however, twice daily dosing provides better therapeutic response than once daily dosing.

VIDEX EC: Adolescent/Adult dose: Body weight > 60 kg: 400 mg once daily. Body weight < 60 kg: 250 mg once daily.

Major Toxicities

More common: Diarrhea, abdominal pain, nausea and vomiting.

Less common (more severe): Peripheral neuropathy (dose related), electrolyte abnormalities, and hyperuricemia. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Rare: Pancreatitis (dose related, less common in children than adults), increased liver enzymes, and retinal depigmentation.

Drug Interactions

- Possible decrease in absorption of ketoconazole, itraconazole, and dapsone; administer at least two hours before or two hours after ddI.
- Tetracycline and iron salts should be given one hour before or four hours after ddI.
- Fluoroquinolone antibiotic absorption significantly decreased (chelation of drug by antacid in pediatric powder and tablets); administer two hours before or four to eight hours after ddI (varies with fluoroquinolone antibiotic).
- Concomitant administration of ddI and DLV may decrease the absorption of these drugs; separate dosing by at least two hours.
- Administration with PIs: IDV should be administered at least one hour before ddI on an empty stomach. RTV should be administered at least two hours before or after ddI. NFV should be administered at least one hour after ddI.
- Tenofovir should be administered two hours before or one hour after ddI. The combination may cause increased ddI levels and therefore a higher risk of toxicity.

Special Instructions

- ddI formulation contains buffering agents or antacids.
- Food decreases absorption; administer ddI on an empty stomach (30 minutes before or two hours after a meal). Further evaluation in children regarding administration with meals is under study.
- For oral solution: shake well and keep refrigerated; admixture is stable for 30 days.
- When administering chewable tablets, at least two tablets should be administered to ensure adequate buffering capacity (i.e. if the child's dose is 50 mg, administer two 25 mg tablets and not one 50 mg tablet).
- Buffered powder is not suitable for once daily dosing except in patients with renal impairment.
- Decreased dosage should be used for patients with impaired renal function.

Lamivudine (3TC, Epivir®, Epivir HBV®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations:
- Solution: 5 mg/mL (Epivir HBV), 10 mg/mL;
- Tablets: 100 (Epivir HBV), 150, 300 mg.

Tablets in combination with zidovudine: COMBIVIR-300 mg zidovudine and 150 mg lamivudine.

Tablets in combination with zidovudine and abacavir: TRIZIVIR-300 mg zidovudine, 150 mg lamivudine, and 300 mg abacavir.

Dosage

Neonatal dose (infants aged < 30 days): 2 mg per kg of body weight twice daily.

Pediatric dose: 4 mg per kg of body weight twice daily.

Adolescent/Adult dose: Body weight ≥ 50 kg: 150 mg twice daily or 300 mg once daily. Body weight < 50 kg: 2 mg per kg of body weight twice daily.

Adolescent/Adult dose of COMBIVIR: one tablet twice daily.

Adolescent/Adult dose of TRIZIVIR: one tablet twice daily.

Major Toxicities

More common: Headache, fatigue, nausea, diarrhea, skin rash, and abdominal pain.

Less common (more severe): Pancreatitis (primarily seen in children with advanced HIV infection receiving multiple other medications), peripheral neuropathy, decreased neutrophil count, and increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Drug Interactions

- Trimethoprim/sulfamethoxazole (TMP/SMX) increases 3TC blood levels (possibly competes for renal tubular secretion); unknown significance.
- When used with ZDV may prevent emergence of ZDV resistance, and for ZDV-resistant virus, revision to phenotypic ZDV sensitivity may be observed.

Special Instructions

- Can be administered with food.
- For oral solution: store at room temperature.
- Decrease dosage in patients with impaired renal function.

Stavudine (d4T, Zerit®, Zerit XR®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Solution: 1 mg/mL; Capsules: 15, 20, 30 and 40 mg; Extended-release capsules (Zerit XR): 75 and 100 mg.

Dosage

Neonatal dose: Under evaluation in Pediatric AIDS Clinical Trial Group protocol 332.

Pediatric dose: 1 mg per kg of body weight every 12 hours (up to weight of 30 kg).

Adolescent/Adult dose: Body weight ≥ 60 kg:40 mg twice daily. Body weight < 60 kg: 30 mg twice daily.

Zerit XR capsules (adult dose): Body weight ≥ 60 kg: 100 mg once daily. Body weight < 60 kg: 75 mg once daily.

Major Toxicities

More common: Headache, gastrointestinal disturbances, and skin rashes.

Less common (more severe): Peripheral neuropathy and pancreatitis. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Rare: Increased liver enzymes.

Drug Interactions

- Drugs that decrease renal function could decrease clearance.
- Should not be administered in combination with ZDV (poor antiretroviral effect).

Special Instructions

- Can be administered with food.
- Need to decrease dose in patients with renal impairment.
- For oral solution: shake well and keep refrigerated; solution stable for 30 days.

Tenofovir (Viread®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Tablets: 300 mg

Dosage

Neonatal dose: Unknown

Pediatric dose: Safety and effectiveness in pediatric patients have not been established. Current indication is for patients 18 years of age and older. Phase I study in pediatric patients is underway.

Adult dose: 300 mg once daily.

Major Toxicities

More common: Nausea, diarrhea, vomiting and flatulence.

Less common (more severe): Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported with the use of nucleoside analogs.

Rare (unknown): Tenofovir caused bone toxicity (osteomalacia and reduced bone density) in animals when given in high doses. These effects have not been seen in adult patients taking tenofovir for up to one year. It is not known if these effects will be seen in persons taking tenofovir for more than one year or in children. Evidence of renal toxicity including increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and/or calcuria and decreases in serum phosphate has been observed in animal studies at high exposure levels. Tenofovir-associated renal toxicity has not been observed in clinical studies of patients on treatment for up to one year. The long-term renal effects are not known but patients at risk should be closely monitored.

Drug Interactions

- Drugs that decrease renal function or compete for active tubular secretion could reduce clearance of tenofovir.
- ddI serum concentrations are increased when co-administered with tenofovir and patients should be monitored for ddI toxicity.
- Tenofovir should be given two hours before or one hour after ddI formulations.

Special Instructions

- Administer with food. High fat meal increases absorption.
- Decreased dosage should be used in patients with impaired renal function.
- Tenofovir should not be administered to patients with renal insufficiency (creatinine clearance < 60 mL/min) until prescribing data is available in this patient population.
- Safety and effectiveness in pediatric patients has not been established.

Zalcitabine (ddC, HIVID®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Syrup: 0.1 mg/mL (investigational); Tablets: 0.375 and 0.75 mg.

Dosage

Neonatal dose: Unknown

Pediatric usual dose: 0.01 mg per kg of body weight every eight hours.

Adolescent/Adult dose: 0.75 mg three times a day.

Major Toxicities

More common: Headache, gastrointestinal disturbances, and malaise.

Less common (more severe): Peripheral neuropathy, pancreatitis, hepatic toxicity, oral ulcers, esophageal ulcers, hematologic toxicity, and skin rashes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Drug Interactions

- Cimetidine, amphotericin, foscarnet, and aminoglycosides may decrease renal clearance of ddC.
- Antacids decrease absorption of ddC.
- Concomitant use with ddI is not recommended because of the increased risk of peripheral neuropathy.
- Intravenous pentamidine increases the risk for pancreatitis; do not use concurrently.

Special Instructions

- Because the presence of food may decrease the rate and extent of absorption, it is recommended that ddC be administered on an empty stomach (one hour before or two hours after a meal).
- Decrease dosage in patients with impaired renal function.

Zidovudine (ZDV, AZT, Retrovir®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations:

- Syrup: 10 mg/mL;
- Capsules: 100 mg;
- Tablets: 300 mg;
- Concentrate for injection/for intravenous infusion: 10 mg/mL.

Tablets in combination with lamivudine: COMBIVIR- 300 mg zidovudine and 150 mg lamivudine.

Tablets in combination with lamivudine and abacavir: TRIZIVIR- 300 mg zidovudine, 150 mg lamivudine, and 300 mg abacavir.

Dosage

Dose for premature infants: (Standard neonatal dose may be excessive in premature infants.) 1.5 mg per kg of body weight (intravenous) or 2 mg per kg of body weight (oral) every 12 hours increased to every eight hours at two weeks of age (neonates 30 weeks gestational age) or at four weeks (neonates < 30 weeks gestational age).

Neonatal/Infant dose (infants aged < 90 days): Oral: 2 mg per kg of body weight every six hours. Intravenous: 1.5 mg per kg of body weight every six hours.

Pediatric usual dose: Oral: 160 mg per m^2 of body surface area every eight hours.

Intravenous (intermittent infusion): 120 mg per m^2 of body surface area every six hours.

Intravenous (continuous infusion): 20 mg per m^2 of body surface area per hour.

Pediatric dosage range: 90 mg per m^2 of body surface area to 180 mg per m^2 of body surface area every six to eight hours.

Adolescent/Adult dose: 200 mg three times a day or 300 mg twice daily.

Adolescent/Adult dose of TRIZIVIR: one tablet twice daily.

Major Toxicities

More common: Hematologic toxicity, including granulocytopenia and anemia, and headache.

Less common: Myopathy, myositis, and liver toxicity.

Unusual (severe): Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Drug Interactions

- Increased toxicity may be observed with concomitant administration of the following drugs (therefore, more intensive toxicity monitoring may be warranted): ganciclovir, interferon-alpha, TMP/SMX, acyclovir, and other drugs that can be associated with bone marrow suppression.
- The following drugs may increase ZDV concentrations (and therefore potential toxicity): probenecid, atovaquone, methadone, valproic acid, and fluconazole.
- Decreased renal clearance may be observed with co-administration of cimetidine (may be significant in patients with renal impairment).
- ZDV metabolism may be increased with coadministration of rifampin and rifabutin (clinical significance unknown); clarithromycin may decrease concentrations of ZDV probably by interfering with absorption (preferably administer four hours apart).
- Ribavirin decreases the intracellular phosphorylation of ZDV (conversion to active metabolite).
- Phenytoin concentrations may increase or decrease.
- Should not be administered in combination with d4T (poor antiretroviral effect).

Special Instructions

- Can be administered with food (although the manufacturer recommends administration 30 minutes before or one hour after a meal).
- Decrease dosage in patients with severe renal impairment.
- Substantial granulocytopenia or anemia may necessitate interruption of therapy until marrow recovery is observed; use of erythropoietin, filgrastim, or reduced ZDV dosage may be necessary in some patients.
- Reduced dosage may be indicated in patients with substantial hepatic dysfunction.
- Infuse intravenous loading dose or intermittent infusion dose over one hour.
- *For intravenous solution:* dilute with 5 percent dextrose injection solution to concentration <4 mg/mL; refrigerated diluted solution is stable for 24 hours.
- Some experts in pediatric HIV infection use a dose of 180 mg per m^2 of body surface area every 12 hours when using in drug combinations with other antiretroviral compounds, but data on this dosing in children is limited.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS (NNRTIS) *

*Information in this appendix is not all-inclusive. Complete and detailed prescribing and toxicity information on these drugs is available from the drug companies and should be reviewed by the health-care provider before prescribing these drugs.

Delavirdine (DLV, Rescriptor®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Tablets: 100 mg and 200 mg.

Dosage

Neonatal dose: Unknown.

Pediatric dose: Unknown.

Adolescent/Adult dose: 400 mg three times a day or 600 mg twice daily (investigational).

Major Toxicities

More common: Headache, fatigue, gastrointestinal complaints, and rash (may be severe).

Drug Interactions

- Metabolized in part by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- DLV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. DLV is not recommended for concurrent use with antihistamines (i.e. astemizole or terfenadine), sedative-hypnotics (i.e. alprazolam, midazolam, or triazolam), calcium channel blockers (i.e. nifedipine), ergot alkaloid derivatives, amphetamines, cisapride, or warfarin.
- DLV clearance is increased, resulting in substantially reduced concentrations of DLV, with concurrent use of rifabutin, rifampin, or anticonvulsants (i.e. phenytoin, carbamazepine, or phenobarbital). Concurrent use is not recommended.
- Absorption of DLV is decreased if given with antacids or histamine^2 receptor antagonists.
- Increased through concentrations of DLV if given with ketoconazole or fluoxetine; increased levels of both drugs if DLV is given with clarithromycin.
- DLV increases levels of dapsone and quinidine.
- Administration with protease inhibitors: decreases metabolism of SQV and IDV, resulting in a significant increase in SQV and IDV concentrations and a slight decrease in DLV concentrations.

Special Instructions

- Can be administered with food.
- Should be taken one hour before or one hour after ddI or antacids.
- The 100 mg tablets can be dissolved in water and the resulting dispersion taken promptly. However, the 200 mg tablets should be taken as intact tablets, because they are not readily dispersed in water.

Efavirenz (DMP-266, EFV, Sustiva™)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Capsules: 50, 100, and 200 mg. Tablets: 600 mg

Dosage

Neonatal dose: Unknown

Pediatric dose: Administered once daily. Body weight 10 to < 15 kg: 200 mg; 15 to < 20 kg: 250 mg; 20 to < 25 kg: 300 mg; 25 to < 32.5 kg: 350 mg; 32.5 to < 40 kg: 400 mg; > 40 kg: 600 mg. There are currently no data available on the appropriate dosage for children under age three years.

Adult/Adolescent dose: 600 mg once daily

Major Toxicities

More common: Skin rash; central nervous system (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria), primarily reported in adults; increased aminotransferase levels, teratogenic in primates (use in pregnancy should be avoided and women of childbearing potential should undergo pregnancy testing before initiating therapy).

Drug Interactions

- Mixed inducer/inhibitor of cytochrome P450 3A4 enzymes; concentrations of concomitant drugs can be increased or decreased depending on specific enzyme pathway involved.
- Not recommended for concurrent use: antihistamines (i.e. astemizole or terfenadine), sedative-hypnotics (i.e. midazolam or triazolam), cisapride, or ergot alkaloid derivatives.
- Drug interactions requiring careful monitoring if co-administered: warfarin (levels potentially increased or decreased); ethinyl estradiol (levels potentially increased; while of uncertain clinical significance, a reliable method of barrier contraception should be used in addition to oral contraceptives).
- Enzyme inducers such as rifampin, rifabutin, phenobarbital and phenytoin may decrease EFV concentrations; clinical significance is unknown.
- EFV is highly plasma protein bound, and has the potential for drug interactions with other highly proteinbound drugs (i.e. phenobarbital and phenytoin).
- Clarithromycin levels are decreased while the levels of its metabolite are increased; alternatives to clarithromycin, such as azithromycin, should be considered. Other macrolide antibiotics have not been studied in combination with EFV.
- Numerous drug interactions when EFV is administered in combination with protease inhibitors: Co-administration decreases levels of SQV (area under the curve [AUC] decreased by 50%) and IDV (AUC decreased by 31%). Co-administration of SQV as a sole PI is not recommended; IDV dose should be increased if given with EFV (for adults, from 800 mg to 1000 mg every eight hours). Co-administration increases levels of both RTV and EFV (AUC increased by 20 percent for both), and is associated with a higher frequency of adverse clinical and laboratory findings; monitoring of liver enzymes is recommended if co-administered. Coadministration increases levels of NFV (AUC increased by 20%) but no dose adjustment is needed. EFV lowers LPV/r plasma concentrations and higher

doses of LPV/r are recommended when used in combination.

Special Instructions

- Efavirenz can be taken with and without food. The relative bioavailability of EFV was increased by 50 percent (range 11-126%) following a high fat meal (1070 kcal, 82 grams fat, 62% of calories from fat-this is equivalent to an intake of 8.2 Milky Way candy bars in one sitting). Because there is no information on safety of EFV when given above the recommended dose, administration with a high fat meal should be avoided due to the potential for increased absorption.
- Capsules may be opened and added to liquids or foods, but EFV has a peppery taste; grape jelly has been used to disguise the taste.
- Bedtime dosing is recommended, particularly during the first two to four weeks of therapy, to improve tolerability of central nervous system side effects.

Nevirapine (NVP, Viramune®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Suspension: 10 mg/mL; Tablets: 200 mg.

Dosage

NVP is initiated at a lower dose and increased in a stepwise fashion. This allows induction of cytochrome P450 3A which results in increased clearance of drug. The occurrence of rash may be diminished by the stepwise increase in dosage. The following suggested incremental increases in dose are given for days on treatment (not age).

Neonatal dose (through age two months): Under study in Pediatrics AIDS Clinical Trial Group protocol 356: 5 mg/kg of body weight or 120 mg/m^2 of body surface area once daily for 14 days, followed by 120 mg/m^2 of body surface area every 12 hours for 14 days, followed by 200 mg/m^2 of body surface area every 12 hours.

*Pediatric dose:** 120-200 mg/m^2 every 12 hours. Note: Initiate therapy with 120 mg/m^2 (maximum 200 mg) administered once daily for 14 days. Increase to full dose (120-200 mg/m^2) administered every 12 hours (maximum 200 mg every 12 hours) if no rash or other untoward effects.

or

- 7 mg/kg every 12 hours < eight years of age
- 4 mg/kg every 12 hours > eight years of age

Note: Initiate therapy with daily dose for 14 days and increase to full dose if no rash or other untoward effects.

Adolescent/Adult dose: 200 mg every 12 hours. Note: Initiate therapy with 200 mg given once daily for the first 14 days. Increase to full dose administered every 12 hours if there is no rash or other untoward effects.

Major toxicities: (continuous dosing, not single dose regimens)

More common: (similar to adults) Skin rash (some severe, requiring hospitalization, and life-threatening, including Stevens-Johnson syndrome, toxic epidermal necrolysis), fever, nausea, headache, and abnormal liver function tests.

Less common: Inflammation of the liver (hepatitis), which rarely may lead to severe and life threatening and in some cases fatal liver damage, and very rarely fatal liver failure and granulocytopenia. Hypersensitivity reactions (including, but not limited to, severe rash or rash accompanied by fever, blisters, oral lesions, conjunctivitis, facial edema, muscle or joint aches, general malaise and/or significant hepatic abnormalities).

Drug Interactions

- Induces hepatic cytochrome P450 3A (CYP3A); auto-induction of metabolism occurs in two to four weeks with a 1.5 fold to two-fold increase in clearance. There could potentially be multiple drug interactions.**
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- *Administration with PIs:* IDV and SQV (hard and soft gel formulations) concentrations are decreased significantly (approximately 25-30%) when administered with NVP. SQV-HGC (Invirase) is not recommended for use in children and is recommended only in combination with RTV in adults. The adult guidelines recommend that IDV doses be increased by 20 percent when administered in combination with NVP, while recommending standard doses of NFV or RTV in combination with NVP. Data on specific dosing adjustments in pediatric patients for both IDV and NFV are lacking. NVP lowers LPV/r concentrations and higher doses of LPV/r are recommended when used in combination.
- *Antifungals:* NVP significantly reduces ketoconazole concentrations and these drugs should not be used concomitantly. If indicated, an alternate antifungal agent, such as fluconazole, should be used.
- *Rifampin/Rifabutin:* Rifampin significantly decreases NVP concentrations. It is not recommended that these drugs be used together. Rifabutin has less of an effect on NVP concentrations.
- *Methadone:* Patients on methadone maintenance may experience narcotic withdrawal symptoms when NVP is added to their regimen. If withdrawal symptoms occur, methadone doses should be increased and titrated to patient response.
- *Anticonvulsants and psychotropics:* There are no data on the extent of drug interactions with the anticonvulsants phenobarbital, phenytoin, and carbamazepine. Serum concentrations of these agents should be monitored. Many of the psychotropics are metabolized by similar metabolic pathways as NVP and may interact; patients should be monitored carefully when these medications are used concomitantly.

- *Oral contraceptives:* NVP may reduce plasma concentrations of oral contraceptives and other hormonal contraceptives. Oral contraceptives should not be the only means of birth control when used in patients on NVP.

Special Instructions

- Can be administered with food.
- May be administered concurrently with ddI.
- NVP-associated skin rash usually occurs within the first six weeks of therapy. If rash occurs during the initial 14-day lead-in period, do not increase dose until rash resolves. NVP should be discontinued immediately in patients who develop severe rash or a rash accompanied by constitutional symptoms (i.e. fever, oral lesions, conjunctivitis, or blistering).
- Severe, life-threatening and in some cases fatal, hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure, has been reported in NVP-treated patients. Increased serum transaminase levels or a history of hepatitis B or C infection prior to starting NVP are associated with higher risk for hepatic adverse events. The majority of cases have occurred during the first 12 weeks of NVP therapy, and frequent and intensive clinical and laboratory monitoring, including liver function tests, is important during this time period. However, about one third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and progressed to hepatic failure; patients with symptoms or signs of hepatitis should have liver function tests performed. Patients should be instructed to contact their HIV specialist if signs or symptoms develop to determine the need for evaluation. NVP should be permanently discontinued and not restarted in patients who develop clinical hepatitis.
- For suspension: Must be shaken well; store at room temperature.

*The majority of clinical trials involving infants and children utilized the 120-200 mg/m^2 dosing regimen. The new FDA approved regimen, which uses mg/kg dosing, is based on pharmacokinetic modeling designed to achieve similar plasma concentrations as dosing of 150 mg/m^2. NVP clearance is highest during the first two years of life, decreasing gradually after eight to 12 years of age and approaching adult clearance rates. The new dosing regimen accounts for the changes in clearance that occurs after eight years of age. However, the changes in clearance are gradual and the new mg/kg dosing regimen results in an abrupt 43 percent decrease in dose size when the 8th birthday is reached. Some clinicians may prefer the mg/m^2 dosing that was utilized in clinical trials.

** Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, with multiple drugs. Some of which may be life-threatening. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health-care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

< FNID = CHAPTER21FN2† Adolescents in early puberty (Tanner I-II) should be dosed using pediatric schedules, whereas those in late puberty (Tanner Stage V) should be dosed using adult schedules. Youth who are in the midst of their growth spurt (Tanner III females and Tanner IV males) should be closely monitored for medication efficacy and toxicity when choosing adult or pediatric dosing guidelines.

Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening with multiple drugs. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health-care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

Protease Inhibitors (PIs)*

*Information in this appendix is not all inclusive. Complete and detailed prescribing and toxicity information on these drugs is available from the drug companies and should be reviewed by the health-care provider before prescribing these drugs.

Amprenavir (APV, Agenerase™)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Pediatric oral solution: 15 mg/mL; Capsules: 50 and 150 mg.

Dosage

Neonatal/infant dose: Not recommended in children < 4 years of age.

Pediatric/Adolescent dose (< 50 kg): For children 4-12 years of age or 13-16 years olds weighing less than 50 kg: Oral Solution: 22.5 mg/kg twice daily hours or 17 mg/kg three times daily (maximum daily dose 2,800 mg). Capsules: 20 mg/kg twice daily or 15 mg/kg three times daily (maximum daily dose 2,400 mg).

Adult dose: 1,200 mg (eight 150 mg capsules) bid

Combination with ritonavir (adults): APV 600 mg + RTV 100 mg twice daily, or APV 1200 mg + RTV 200 mg once daily.

Major Toxicities

More common: Vomiting, nausea, diarrhea, perioral parethesias, and rash.

Less common (more severe): Life-threatening rash, including Stevens-Johnson syndrome in 1 percent of patients.

Rare: Increased cholesterol levels, new onset diabetes mellitus, hyperglycemia, exacerbation of preexisting diabetes mellitus, hemolytic anemia, and spontaneous bleeding in hemophiliacs.

Drug Interactions

- APV is a substrate for and inhibitor of the cytochrome P450 isoenzyme CYP3A4. There could potentially be multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Co-administering EFV and APV lowers levels of APV 39 percent.
- APV should not be administered concurrently with astemizole, bepridil, cisapride, dihydroergotamine, ergotamine, midazolam, rifampin and triazolam.
- Although no interaction studies have been conducted, serious drug interactions could occur between amiodarone, lidocaine, tricyclic antidepressants, quinidine and warfarin. It is recommended that the concentration of these drugs be monitored when administered concomitantly with APV.
- Rifampin has been found to reduce plasma concentrations of APV (decreased AUC 82%) and should not be used with APV. APV has no significant effect on rifampin plasma levels.
- The AUC of rifabutin is increased by 193 percent when given in combination with APV. The dose of rifabutin should be reduced by at least half the recommended dose when given in combination with APV.
- Co-administration of APV with sildenafil (Viagra) is likely to result in increased sildenafil concentrations and patients should be advised that they may be at an increased risk for sildenafil-associated adverse events, including hypotension, visual changes, and priapism.
- The FDA approved formulation of APV contains 46 IU vitamin E/ml of oral solution and 109 IU vitamin E-150 mg capsule. The recommended dose of APV results in a dose of 138 IU/kg/day of vitamin E using the oral solution with a maximum dose of 8,587 IU vitamin E per day. Patients receiving the recommended adult dose of APV in capsule form receive 1,744 IU/day of vitamin E. In comparison, the daily recommended dose for vitamin E in children is 10 IU per day and in adults 30 IU per day. Excess ingestion or administration of vitamin E has been associated with creatinuria, decreased platelet aggregation, impaired wound healing, hepatomegaly, prolongation of the Prothrombin Time and the potentiation of vitamin K deficiency coagulopathy. High dose vitamin E may increase the hypoprothrombinemic response to drugs such as warfarin and dicumarol and concurrent use of vitamin E doses > 400 IU/day should be avoided in patients taking oral anticoagulants. Patients taking APV should be advised not to take supplemental vitamin E.
- The liquid formulation of APV contains propylene glycol in a concentration that exceeds WHO standards for use in infants. The serum half-life of propylene glycol in neonates is prolonged at 16.9 hours compared to five hours in adults, due to the immaturity of alcohol dehydrogenase enzyme activity in young infants. High levels of propylene glycol have been associated with hyperosmolarity, lactic acidosis, seizures, and respiratory depression.
- The efficacy of hormonal contraceptives may be reduced in patients receiving APV. Alternate or additional methods of birth control should be co-administered if co-administering with hormonal methods of birth control.
- Other medications that are substrates, inhibitors, or inducers of CYP3A4 could also potentially interact with APV. See the product information for Agenerase for complete list of other drugs, which may potentially interact with APV.
- APV is a sulfonamide. The potential for cross sensitivity between drugs in the sulfonamide class and APV is unknown. APV should be used with caution in patients with sulfonamide allergy.

Special Instructions

- APV should not be used in children less than four years of age because of the lack of data in children < 4 years of age, the paucity of data in children in general, the uncertain impact of extremely high doses of vitamin E, and the propylene glycol content of the oral liquid preparation.
- The oral solution and capsule formulation are not interchangeable on a mg per mg basis. The oral bioavailability of the oral solution is 14 percent less than that of the capsule.
- APV may be taken with or without food, but should not be given with a high fat meal (i.e. 6.7 Milky Way bars) as there is a 21 percent decrease in the AUC when APV is administered after a high fat meal of 67 grams of fat compared with the fasting state.
- Patients taking antacids (or ddI) should take APV at least one hour before or after antacid (or ddI) use.

Indinavir (IDV, Crixivan®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Capsules: 200 and 400 mg.

Dosage

Neonatal dose: Unknown. Due to side effect of hyperbilirubinemia, should not be given to neonates until further information is available.

Pediatric dose: Under study in clinical trials: 500 mg per m^2 of body surface area every eight hours. Patients with small body surface areas may require lower doses (300-400 mg/m2 every 8 hours).

Adolescent/Adult dose: 800 mg every eight hours.

Combination with ritonavir (adults): IDV 400 mg + RTV 400 mg twice daily, or IDV 800 mg + RTV 200 mg twice daily.

Combination with efavirenz (adults): IDV 1000 mg three times daily + EFV 600 mg once daily.

Major Toxicities

More common: Nausea, abdominal pain, headache, metallic taste, dizziness and asymptomatic hyperbilirubinemia (10%).

Less common (more severe): Nephrolithiasis (4%) and exacerbation of chronic liver disease.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis, diabetes and hemolytic anemia.

Drug Interactions

- Cytochrome P450 3A4 (CYP3A4) responsible for metabolism. There could potentially be multiple drug interactions.
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- IDV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. IDV is not recommended for concurrent use with antihistamines (i.e. astemizole or terfenadine), cisapride, ergot alkaloid derivatives, or sedative-hypnotics (i.e. triazolam or midazolam).
- IDV levels are significantly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin concentrations are increased, therefore a dose reduction of rifabutin to half the usual daily dose is recommended.
- Ketoconazole and itraconazole cause an increase in IDV concentrations (consider reducing adolescent/adult IDV dose to 600 mg every eight hours).
- Co-administration of clarithromycin increases serum concentration of both drugs (dosing modification not needed).
- Co-administration of NVP or EFV may decrease IDV serum concentration.
- Administration with other PIs: coadministration with NFV increases concentration of both drugs; coadministration with SQV increases concentration of SQV.

Special Instructions

- Administer on an empty stomach one hour before or two hours after a meal (or can take with a light meal).
- When given in combination with RTV, meal restrictions are no longer necessary.
- Adequate hydration required to minimize risk of nephrolithiasis (at least 48 oz of fluid daily in adult patients).
- If co-administered with ddI, give at least one hour apart on an empty stomach.
- Decrease dose in patients with hepatic insufficiency.
- Capsules are sensitive to moisture and should be stored in original container with desiccant.

Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening, with multiple drugs. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health-care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

Lopinavir/Ritonavir (Kaletra,™ ABT 378, LPV/RTV)

URL: Link to Pediatric Antiretroviral Drug Information

Conformulation of lopinavir and ritonavir: RTV acts as a pharmacokinetic enhancer, not as an antiretroviral agent. It does this by inhibiting the metabolism of lopinavir and increasing lopinavir plasma concentrations.

Preparations: Pediatric oral solution: 80 mg lopinavir and 20 mg ritonavir per mL; Capsules: 133.3 mg lopinavir/33.3 mg RTV.

Dosage

Neonatal dose: No pharmacokinetic data on dosing children less than six months of age.

- For individuals not receiving concomitant nevirapine or efavirenz:

Pediatric Dose

Six months to 12 years of age (without NVP or EFV)

7 to < 15 kg	12 mg per kg lopinavir/3 mg per kg ritonavir twice daily with food.
15 to 40 kg	10 mg per kg lopinavir/2.5 mg per kg ritonavir twice daily with food.
> 40 kg	400 mg lopinavir/100 mg ritonavir (three capsules or 5 mL) twice daily with food (same as adult dose).

OR

230 mg per m^2 lopinavir/57.5 mg per m^2 ritonavir twice daily with food, up to a maximum of 400 mg lopinavir/100 mg RTV.

Adult/Adolescent dose: 400 mg lopinavir/100 mg ritonavir (three capsules or 5 mL) twice daily with food.

- For individuals receiving concomitant NVP or EFV (which induce lopinavir metabolism, reduce plasma levels and require increased lopinavir/ritonavir dosing) and/or treatment-experienced patients where reduced susceptibility to lopinavir is suspected (such as those with prior treatment with other PIs):

Pediatric Dose

Six months to 12 years of age (with NVP or EFV)

7 to < 15 kg	13 mg per kg lopinavir/3.25 mg per kg ritonavir twice daily with food.
15 to 50 kg	11 mg per kg lopinavir/2.75 mg per kg ritonavir twice daily with food.

> 50 kg 533 mg lopinavir/133 mg ritonavir (four capsules or 6.5 mL) twice daily with food (same as adult dose).

OR

300 mg per m^2 lopinavir/75 mg per m^2 ritonavir twice daily with food up to a maximum of 533 mg lopinavir/133 mg ritonavir.

Adult/Adolescent dose: 533 mg lopinavir/133 mg ritonavir (four capsules or 6.5 mL) twice daily with food.

Note: Although pediatric clinical trials utilized the mg per m^2 body surface area dosing, the FDA-approved doses are based on a mg per kg body weight dosage. The 230 mg per m^2 lopinavir/57.5 mg per m^2 RTV twice daily regimen without NVP or EFV and the 300 mg per m^2 lopinavir/75 mg per m^2 ritonavir twice daily regimen with concomitant NVP or EFV resulted in lopinavir concentrations similar to those obtained in adults receiving the 400 mg lopinavir/100 mg ritonavir twice daily regimen (without concomitant NVP or EFV). The pediatric trials were done in NNRTI naïve patients and there is little data in heavily pre-treated pediatric patients. In treatment-experienced patients where reduced susceptibility to lopinavir is suspected, higher doses may be required but there is little data to make definitive dosing recommendations at this time.

Major Toxicities

More common: Diarrhea, headache, asthenia, and nausea and vomiting. Increase in blood lipids (cholesterol and triglycerides), and rash in patients receiving lopinavir/ritonavir with other antiretroviral drugs.

Rare: Spontaneous bleeding episodes in hemophiliacs, pancreatitis, hyperglycemia, ketoacidosis, diabetes, and hepatitis.

Drug Interactions

- Lopinavir/ritonavir is extensively metabolized by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions. *
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Drugs that should not be co-administered with lopinavir/ritonavir include: antiarrhythmics (i.e., flecainide, propafenone); ergot alkaloid derivatives; antihistamines (i.e. astemizole, terfenadine); cisapride; neuroleptics (i.e. pimozide); sedative-hypnotics (i.e. midazolam, triazolam); HMG-COA reductase inhibitors (i.e. lovastatin, simvastatin); rifampin and St. John's wort.
- EFV and NVP induce the metabolism of lopinavir and decrease plasma concentrations. A dose increase of lopinavir/ritonavir is recommended (see dosage section).
- Anticonvulsant drugs including carbamazepine, phenytoin, and phenobarbital increase CYP3A activity, leading to increased clearance and, therefore, lower levels of lopinavir, and should be used with caution.
- Dexamethasone decreases lopinavir serum concentrations. Use with caution.
- Lopinavir/ritonavir increases serum concentrations of some HMG-CoA reductase inhibitors (i.e. atorvastatin, cerivastatin). Pravastatin and fluvastatin are preferred alternative agents.
- Lopinavir/ritonavir increases serum clarithromycin concentration and clarithromycin dose adjustment is recommended in patients with impaired renal function (CrCl 30-60 mL/min decrease clarithromycin dose by 50 percent; CrCl < 30 mL/min decrease clarithromycin dose by 75%).
- Lopinavir/ritonavir increases rifabutin and rifabutin metabolite concentrations, and dose reduction of rifabutin by at least 75 percent of the usual dose is recommended.
- Lopinavir/ritonavir increases sildenafil (Viagra) serum concen-trations. Reduce dose of sildenafil and monitor for toxicity.
- Lopinavir/ritonavir increases serum concentrations of the anti-arrhythmics amiodarone, bepridil, lidocaine (systemic) and quinidine. Monitoring of antiarrhythmic serum concentrations is recommended.
- Lopinavir/ritonavir may increase serum concentrations of the immunosuppressant agents cyclosporine, tacrolimus, and rapamycin. Monitor serum concentrations of these agents when co-administered.
- Lopinavir/ritonavir increases serum concentrations of dihydropyridine calcium channel blockers (i.e. felodipine, nifedipine, nicardipine). Clinical monitoring is recommended.
- Lopinavir/ritonavir decreases methadone serum concentrations when coadministered. Patients should be closely monitored for withdrawal symptoms, and methadone dosage should be increased as necessary.
- Lopinavir/ritonavir increases serum concentrations of ketoconazole and itraconazole. High doses of these agents (>200 mg/day) are not recommended.
- Lopinavir/ritonavir decreases atovaquone concentrations. The clinical significance is unknown.
- Ethinyl estradiol levels are reduced by lopinavir/ritonavir, and alternative or additional methods of birth control should be used if coadministered with hormonal methods of birth control.
- Administration with other PIs: appropriate doses of lopinavir/ritonavir with APV, SQV, IDV, or additional RTV have not been established.
- Lopinavir/ritonavir oral solution contains 42.4 percent alcohol and can cause a disulfiram-like reaction when co-administered with disulfiram or metronidazole.

*Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions with multiple drugs, some of which may be life-threatening. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health-care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Administer with food. High fat meal increases absorption, especially of the liquid preparation.
- If coadministered with ddI, ddI should be given one hour before or two hours after lopinavir/ritonavir.
- Oral solution and capsules should be refrigerated. Can be kept at room temperature up to 77°F (25°C) if used within two months.

Nelfinavir (NFV, Viracept®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Powder for oral suspension: 50 mg per one level gram scoop full (200 mg per one level teaspoon); Tablets: 250 mg tablet.

Dosage

Neonatal dose: Under study in Pediatric AIDS Clinical Trials Group protocol 353: 40 mg per kg of body weight every 12 hours.

Pediatric dose: Currently under review: 20 to 30 mg per kg of body weight three times a day is the FDA approved dose. However, doses as high as 45 mg/kg every 8 hours are routinely used. Twice daily dosing in pediatric patients is under study (50-55 mg/kg/dose) in older children (> 6 years of age).

Adolescent/Adult dose: 1250 mg (5 tablets) twice daily or 750 mg (3 tablets) three times daily. Doses of 1500 mg (6 tablets) twice daily are under study in adults.

Major Toxicities

More common: Diarrhea.

Less common: Asthenia, abdominal pain, rash and exacerbation of chronic liver disease.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis and diabetes.

Drug Interactions

- NFV is in part metabolized by cytochrome P450 3A4 (CYP3A4). There could potentially be multiple drug interactions. *
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- NFV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. NFV is not recommended for concurrent use with antihistamines (i.e. astemizole or terfenadine); cisapride; ergot alkaloid derivatives; certain cardiac drugs (i.e. quinidine or amiodarone); or sedative-hypnotics (i.e. triazolam or midazolam).
- NFV levels are greatly reduced with concurrent use of rifampin. Concurrent use is not recommended.
- Rifabutin causes less decline in NFV concentrations; if co-administered with NFV, rifabutin should be reduced to one half the usual dose.
- Estradiol levels are reduced by NFV, and alternative or additional methods of birth control should be used if co-administering with hormonal methods of birth control.
- Co-administration with DLV increases NFV concentrations two fold and decreases DLV concentrations by 50 percent. There are no data on co-administration with NVP, but some experts use higher doses of NFV if used in combination with NVP.
- Administration with other PIs: co-administration with IDV increases concentration of both drugs; co-administration with SQV increases concentration of SQV with little change in NFV concentration; co-administration with RTV increases concentration of NFV without change in RTV concentration.

* Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening, with multiple drugs. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health-care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Administer with meal or light snack.
- If co-administered with ddI, NFV should be administered two hours before or one hour after ddI.
- For oral solution: powder may be mixed with water, milk, pudding, ice cream, or formula (for up to six hours).
- Do not mix with any acidic food or juice because of resulting poor taste.
- Do not add water to bottles of oral powder; a special scoop is provided with oral powder for measuring purposes.
- Tablets readily dissolve in water and produce a dispersion that can be mixed with milk or chocolate milk; tablets also can be crushed and administered with pudding.

Ritonavir (RTV, Norvir®)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Oral solution: 80 mg/mL; Capsules: 100 mg

Dosage

Neonatal dose: Under study in Pediatric AIDS Clinical Trials Group protocol 354 (single dose pharmacokinetics).

Pediatric usual dose: 400 mg per m^2 of body surface area every 12 hours. To minimize nausea/vomiting, initiate therapy starting at 250 mg per m^2 of body surface area every 12 hours and increase stepwise to full dose over five days as tolerated.

Pediatric dosage range: 350 to 400 mg per m^2 of body surface area every 12 hours.

Adolescent/Adult dose: 600 mg twice daily. To minimize nausea/vomiting, initiate therapy starting at 300 mg twice daily and increase stepwise to full dose over five days as tolerated.

Combination with Saquinavir (Fortovase) (adults): RTV 400 to 600 mg + SQV 400 mg twice daily.

Pharmacokinetic enhancer: Used at lower doses as pharmacokinetic enhancer of other protease inhibitors. Doses most commonly used in adults are 200 mg every 12 hours to 400 mg every 12 hours when combined with other protease inhibitors.

Major Toxicities

More common: Nausea, vomiting, diarrhea, headache, abdominal pain, and anorexia.

Less common: Circumoral paresthesias and increase in liver enzymes.

Rare: Spontaneous bleeding episodes in hemophiliacs, pancreatitis, increased levels of triglycerides and cholesterol, hyperglycemia, ketoacidosis, diabetes and hepatitis.

Drug Interactions

- RTV is extensively metabolized by hepatic cytochrome P450 3A (CYP3A). There could potentially be multiple drug interactions.*
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- Not recommended for concurrent use with analgesics (i.e. meperidine, piroxicam, or propoxyphene); antihistamines (i.e. astemizole or terfenadine); certain cardiac drugs (i.e. amiodarone, bepridil hydrochloride, encainide hydrochloride, flecainide acetate, propafenone, or quinidine); ergot alkaloid derivatives; cisapride; sedative-hypnotics (i.e. alprazolam, clorazepate, diazepam, estazolam, flurazepam, midazolam, triazolam, or zolpidem); certain psychotropic drugs (i.e. bupropion hydrochloride, clozapine, or pimozide); rifampin; or rifabutin.
- Estradiol levels are reduced by RTV, and alternative or additional methods of birth control should be used if coadministering with hormonal methods of birth control.
- RTV increases metabolism of theophylline (levels should be monitored, and dose may need to be increased).
- RTV increases levels of clarithromycin (dose adjustment may be necessary in patients with impaired renal function); desipramine (dose adjustment may be necessary); and warfarin (monitoring of anticoagulant effect is necessary).
- RTV may increase or decrease digoxin levels (monitoring of levels is recommended).
- Drugs that increase CYP3A activity can lead to increased clearance and, therefore, lower levels of RTV include carbamazepine, dexamethasone, phenobarbital, and phenytoin (anticonvulsant levels should be monitored because RTV can affect the metabolism of these drugs as well).
- Administration with other PIs: coadministration with SQV and NFV increases concentration of these drugs with little change in RTV concentration.

* Drugs metabolized by the hepatic cytochrome P450 enzyme system have the potential for significant interactions, some of which may be life-threatening, with multiple drugs. These interactions are outlined in detail in prescribing information available from the drug companies. These interactions will not be reiterated in this document, and the health-care provider should review those documents for detailed information. Before therapy with these drugs is initiated, the patient's medication profile should be carefully reviewed for potential drug interactions.

Special Instructions

- Administration with food increases absorption and helps decrease gastrointestinal side effects.
- If RTV is prescribed with ddI, there should be two hours between taking each of the drugs.
- Oral solution must be kept refrigerated and stored in original container; can be kept at room temperature if used within 30 days. Limited shelf-life (six months). Use by product expiration date.
- To minimize nausea, therapy should be initiated at a low dose and increased to full dose over five days as tolerated.
- Techniques to increase tolerance in children: a) mixing oral solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream; b) dulling the taste buds before administration by chewing ice, giving popsicles or spoonfuls of partially frozen orange or grape juice concentrates; c) coating the mouth by giving peanut butter to eat before the dose; or d) administration of strong-tasting foods such as maple syrup, cheese, or strong-flavored chewing gum immediately after dose.

Saquinavir (SQV, Invirase™ Hard Gel Capsule and Fortovase™ Soft Gel Capsule)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Soft gel capsules: 200 mg (preferred product); Hard gel capsules: 200 mg. Please note that Saquinavir-HGC (Invirase) is not recommended except in combination with ritonavir.

Dosage

Neonatal dose: Unknown.

Pediatric dose: Under study: 50 mg per kg body weight every 8 hours as single protease inhibitor therapy. 33 mg per kg body weight every 8 hours as usual therapy with nelfinavir.

Adolescent/Adult dose: Soft gel capsules: 1200 mg three times a day or 1600 mg twice daily.

Major Toxicities

More common: Diarrhea, abdominal discomfort, headache, nausea, paresthesias, and skin rash.

Less common: Exacerbation of chronic liver disease.

Rare: Spontaneous bleeding episodes in hemophiliacs, hyperglycemia, ketoacidosis and diabetes.

Drug Interactions

- SQV is metabolized by the cytochrome P450 3A4 (CYP3A4) system in the liver, and there are numerous potential drug interactions. *
- Before administration, the patient's medication profile should be carefully reviewed for potential drug interactions.
- SQV decreases the metabolism of certain drugs, resulting in increased drug levels and potential toxicity. SQV is not recommended for concurrent use with antihistamines (i.e. astemizole or terfenadine); cisapride; ergot alkaloid derivatives, or sedative-hypnotics (i.e. midazolam or triazolam).
- SQV levels are significantly reduced with concurrent use of rifampin (decreases SQV levels by 80%), rifabutin (decreases SQV levels by 40%), and NVP (decreases SQV levels by 25%).
- SQV levels are decreased by carbamazepine, dexamethasone, phenobarbital, and phenytoin.
- SQV levels are increased by DLV and ketoconazole.
- SQV may increase levels of calcium channel blockers, clindamycin, dapsone, and quinidine. If used concurrently, patients should be closely monitored for toxicity.
- *Administration with other PIs:* coadministration with IDV, RTV, or NFV increases concentration of SQV with little change in concentration of the other drug.

Special Instructions

- Administer within two hours of a full meal to increase absorption.
- Concurrent administration of grapefruit juice increases SQV concentration.
- Sun exposure can cause photosensitivity reactions; therefore, sunscreen or protective clothing is recommended.
- Fortovase® and Invirase® are not bioequivalent and cannot be used interchangeably. Fortovase® is the recommended formulation.

Fusion Inhibitors

Enfuvirtide (Fuzeon™, T-20)

URL: Link to Pediatric Antiretroviral Drug Information

Preparations: Injection: lyophilized powder for injection 108 mg of enfuvirtide, when reconstituted with 1.1 mL sterile water to deliver 90 mg/mL.

Convenience Kit: 60 single use vials of Fuzeon (90 mg strength), 60 vials of sterile water for injection, 60 reconstitution syringes (3mL), 60 administration syringes (1 mL), alcohol wipes.

Dosage

Neonatal/infant dose: Not approved for use in pediatric patients below the age of 6 years old.

Pediatric/adolescent dose (6-16 years of age): 2 mg/kg twice daily, maximum dose 90 mg (1mL) twice daily injected subcutaneously into the upper arm, anterior thigh, or abdomen.

Adolescent/Adult dose: Soft gel capsules: 1200 mg three times a day or 1600 mg twice daily.

Major Toxicities

More common: Almost all patients (98%) get local injection site reactions including pain and discomfort, induration, erythema, nodules and cysts, pruritis, and ecchymosis. Usually mild to moderate in severity but can be more severe.

Less common: Increased rate of bacterial pneumonia (unclear association).

Rare: Hypersensitivity reactions including fever, nausea and vomiting, chills, vigors, hypotension, elevated liver transaminases. Immune-mediated reactions including primary immune complex reaction, respiratory distress, glomerulonephritis, and Guillan-Barre syndrome. Patients experiencing hypersensitivity reactions should seek immediate medical attention. Therapy should not be restarted following signs and symptoms consistent with hypersensitivity reactions.

Drug Interactions

There are no known significant drug interactions.

Special Instructions

- Patients or caregivers should be carefully instructed in proper technique for drug reconstitution and administration of subcutaneous injections. Fuzeon injection instructions are provided with convenience kits.
- Reconstituted vial should be allowed to stand until the powder goes completely into solution which could take up to 45 minutes.
- Once reconstituted, Fuzeon should be injected immediately or kept refrigerated in the original vial until use. Reconstituted Fuzeon must be used within 24 hours.
- Each injection should be given at a site different from the preceding injection site, and should not be injected into moles, scar tissue, bruises, or the navel.
- Careful monitoring for signs and symptoms of local infection or cellulitis should be done by both the patient/caregiver and health care provider.
- Patients/caregivers should be advised of the possibility of a hypersensitivy reaction and should discontinue treatment and seek immediate medical attention if the patient develops signs and symptoms consistent with a hypersensitivity reaction.

Section Ten

Neurological Issues

CHAPTER

85

Pediatric Head Injury

Sandeep Chopra, Manish Vaish, Praveen Khilnani

Exact incidence of head injuries in India is not available, but in the USA incidence is 200 cases/10,000 population.

Children younger than 4 years of age have been reported to have poor prognosis similar to adults while better outcomes have been reported in 5 to 15 year age group.[1]

Open fontanelle and sutures predispose a child to a higher incidence of subdural hematoma (SDH). A possible explanation may be that in an skull that can expand, clinical significant volume of blood can easily gets accumulated and, absence of arachnoid adhesions and pacchioniann granulation's predispose to tearing of bridging veins and accumulation of blood along the vertex.[2]

There is characteric pathognomical brain injury suffered by infants < 3 months of age due to lack of glial tissue, increased brain matter and movable squamosal bones leading to tears of cerebral cortex, mesencephalic dysfunction from cerebral herniation, tears of subcortical white matter and orbito-frontal and temporal lobes.

Older infants suffer from tears at pontomedullary junction, petechial hemorrhages and cellular necrosis. By one year of age sutures are closed and skull becomes rigid. Glial cell proliferation, synaptic connections, and dendrites arborization progress logarithmically till 2 years of age. Myelinization begins at first year and progress till 10th year of life.[3] Hence, contusions, subarachnoid and extradural (epidural) hematoma, and axonal injuries are commonly seen. Diffuse axonal injury is a common cause of persistent coma despite absence of cerebral edema.

Monro-Kellie Doctrine

Since cranial vault is rigid any bleeding or swelling compresses the brain to keep the volume of intracranial vault constant. Therefore ICP in creases Figure 85.1.

Pathogenesis of Brain Injury

After sever traumatic brain injury reduction in cerebral blood flow (CBF) begins almost immediately after injury lasting as long as 24 hours. This happens due to neurochemically mediated vasospasm, astrocyte swelling with compression of the microcirculation. This early hypoperfusion with normal metabolic requirement is a high risk setting and any associated hypotension or hypoxia leads to further hypoxic ischemic injury to the brain. As the injury evolves, blood brain barrier disruption occurs, vasogenic edema occurs. In addition cytotoxic edema is a key factor to secondary cerebral swelling. Enlarging hematoma also contributes to decreased cerebral perfusion pressure (CPP) by increasing the intracranial volume and intracranial pressure (ICP) and decreasing cerebral blood flow. Loss of cerebral autoregulation occurs frequently. Normal cerebral blood flow regulation in response to changes in blood pressure and cerebral vascular tone is absent. Eventually cerebral edema progressively increase the ICP further reducing the CPP (mean arterial pressure (MAP)—intracranial pressure). Aldrich et al[4] reported that incidence of diffuse cerebral swelling was 41 percent in children as compared to 26 percent frequency in adults, possibly due to a hyperemic response (luxury perfusion). Lang et al reported incidence of diffuse cerebral swelling at 4 to 5 times that of adults.[5]

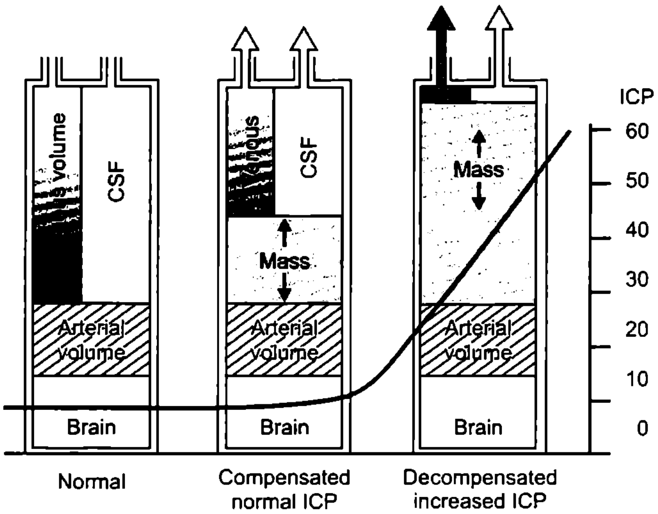


Fig. 85.1: Monro-Kellie doctrine: Cranium is a fixed vault Contains 3 components - Brain 80 percent Blood 10 percent CSF 10 percent. Any bleeding, swelling, mass will lead to increased intracranial pressure (ICP) since volume of the cranial vault is fixed

CLINICAL EVALUATION AND MANAGEMENT IN EMERGENCY

In any child with multiple trauma, a quick primary and secondary survey is performed with prompt attention to airway, breathing and circulation (see chapter on Multiple Trauma). Pediatric patient with head injury may be brought unconscious, posturing (decerebrate or decorticate), or actively convulsing.

Cushings Triad

1. Hypertension
2. Bradycardia and
3. Raised ICP. These three finding may predispose to herniation.

All patients should be presumed to be full stomach and oxygen therapy should be initiated. Comatose patients need to be intubated with rapid sequence intubation technique, (see chapter on Procedures in PICU) with due attention to cervical spine stabilization. Jaw thrust maneuver can be performed during bag mask ventilation.[6] Head tilt and chin lift maneuvers should be avoided. A cervical spine collar should be placed until cervical spine X-rays are obtained to rule out a fracture or dislocation.

Glasgow Coma Scale (GCS): For clinical evaluation, as much as possible, GCS[7,8] for adults should not be used considering the anatomical, physiological and developmental differences of pediatric age group, a modified GCS is available[9] (Table 85.1).

Table 85.1: Modified Glasgow coma scale

Ocular response
1. Pursuit
2. EOM (Extra ocular muscles) intact, reactive pupils
3. Fixed pupils or EOM impaired
4. Fixed pupils and EOM impaired

Verbal response
1. Cries
2. Spontaneous Respiration
3. Apneic

Motor response
1. Flexes and extends
2. Withdraws from painful stimuli
3. Hypertonia
4. Flaccid

Indices of Good Outcome[9-12]

Single most reliable examination for evaluating outcome in children less than 3 years of age is ocular examination, as oculomotor functions are fully developed by two months of age, while cortico spinal myelination and optic pathway myelination develop much later. Child with open fontanel and ocular score of 3-4 generally has good outcome. Similarly children with motor score of 4 and closed fontanel will have good outcome. Those with closed fontanel and verbal score of 3 have good outcome.

Indices of Poor Outcome

Evidence of retinal hemorrhage indicates poor outcome.

Radiographic evidence of post-traumatic splitting of suture indicates poor outcome and high incidence of seizures. A bilateral linear skull fracture correlates with poor outcome. Incidence of post-traumatic seizure is 10 percent in children with depressed fracture and 7 percent without depressed fracture. Occurrence of generalized tonic clonic seizure indicates poor outcome to the extent of 27 to 66 percent.

Irrespective of closed or open fontanel, children with motor neurological deficit like hemiparesis have poor outcome in about 25 percent of cases.

The child has suffered a severe head injury irrespective of child coma score, if any of the following is present:

1. Unequal pupils (a difference of $\geq$ 1 mm)
2. Asymmetric motor examination
3. Open head injury with CSF leak or exposed brain
4. Neurological deterioration (GCS decreased by $\geq$ 2 points)
5. Depressed skull fracture.

External Examination[13,14]

Scalp: Subgaleal/subperiosteal haematoma should be looked for:

Fontanel: To be examined preferably in upright position when child is quiet.

Cranial suture: Metopic, coronal, lambdoid sutures need to be examined for suture width (normally no palpable gap, except for sagittal suture), for mobility, and overlap (normally no overlap is seen).

Heads circumference: Any measurement greater than 2.5 cm, above or below normal value for age is abnormal.

Types of Injuries

Injuries to Scalp

These range from abrasion, sub-galeal or subperiosteal hematoma to laceration of various size, shape and depth, depending upon mode and nature of injury. Major lacerations should be sutured as soon as possible, to prevent further blood loss.

Fractures[15-17]

A. *Linear fracture* Single fracture line passes through entire thickness of skull. A simple linear fracture in itself does not require any intervention. Patient should be placed in PICU observation specially when the fractures lines are crossing over trajectory of meningeal artery or dural sinus. These inoccuous looking fractures may lead to epidural hematoma and gradual deterioration due to oozing from bone or rapid deterioration when arterial bleeding accumulates or severe bleeding from venous sinus occurs.

   Acute epidural hematoma in contrast to adults is as common in posterior meningeal basal territory as it is from middle meningeal artery.

B. *Diastatic fracture*: Linear, Comminuted, Stellate Common in children < 3 years.

   A diastatic linear fracture is break in skull continuity, more specifically sutures, with coarse definite separation of bone edges by > 5 mm over distance of 2 cm. They are potential source of epidural or subdural haematoma or meningocele.

C. *Basilar skull fracture*: Basilar skull fracture may present as raccoon eyes (anterior fracture) or battle sign (petechial hemorrhage over mastoid) in middle cranial fossa fracture). Basilar skull fractures may lead to cerebrospinal fluid (CSF) leak or cerebrocele. With CSF leak chances of meningitis are very high and appropriate meningeal coverage with antibiotics (ceftriaxone and vancomycin) should be considered.

D. *Depressed skull fracture*: Outer table of one or more of the fracture edges lie below normal anatomic level of the inner table as compared to surrounding intact skull. It could be closed or open. An open depressed fracture is surgical emergency.

   Surgery for closed depressed fracture is usually cosmetic but if radiological appearance suggest dural laceration, brain penetration, mass effect, or underlying subdural hematoma, extradural hematoma or intracranial hematoma exploration required.

   In neonates and infants depressed fracture are typically green stick fracture located in frontal or parietal areas. They are called "Ping-Pong" fracture because they show indented bone without fracture in cortical layers. They may resolve spontaneously, fracture > 5 mm may require surgical intervention.

E. *Compound skull fracture* This is a neurosurgical emergency. Once diagnosed clinically, a skull X-ray[18] and CT scan of the head is mandatory. Appropriate management can be undertaken based on findings.

Intracranial Hematoma

Extradural (epidural), subdural, intradural, contusions may be encountered. CT scan of the head is diagnostic and the investigation of choice.

Epidural Hematoma[19] (Figs 85.2 and 85.3)

Epidural hematoma occurs mainly at the convexity or posterior fossa. It could occur due to middle meningeal arterial bleed or tearing of bridging veins.

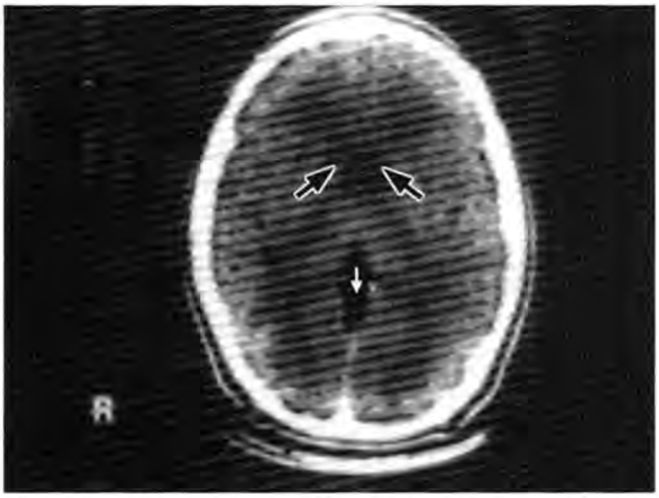


Fig. 85.2: Normal brain—Transaxial CT scan of brain demonstrating normal anatomy at level of frontal horns of lateral ventricles (black arrows). Pineal gland (white arrow) is in normal midline location

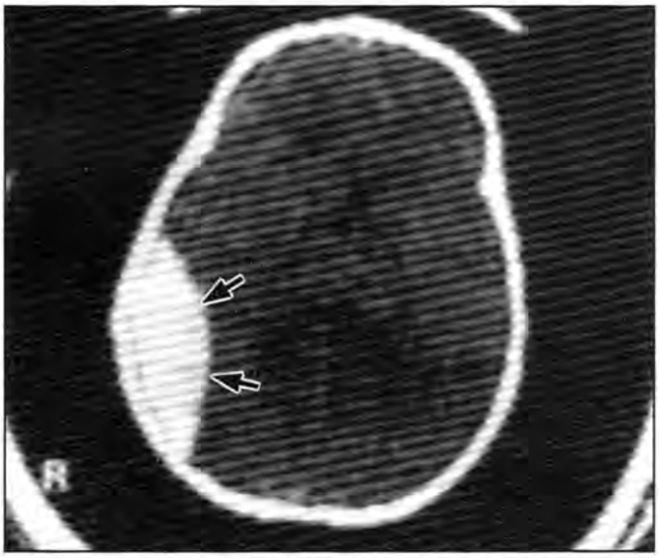


Fig. 85.3: Epidural hematoma—CT scan of brain demonstrating hyperdense right patietal epidural hematoma (black arrows) which has assumed classic lenticular configuration secondary to adherence of data to inner table of skull. Normal brain structures are compressed and shifted

It occurs due to compression/decompression injury, acceleration/deceleration injury or direct trauma and usually present as:

1. Initially normal child coma score followed by pro-gressive deterioration.
2. Initial loss of consciousness, followed by recovery (Lucid interval), followed by loss of consciousness.
3. Continuous progressive deterioration.

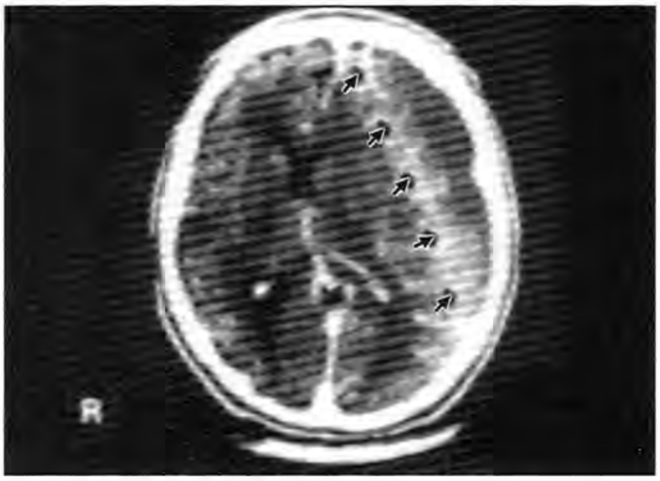


Fig. 85.4: Subacute subdural hematoma—CT scan of brain demonstrating large isodense mass over left cerebral convexity. Compressed cerebral cortex (black arrows) shows enhanced density delineating inner border of subacute subdural hematoma. Normal structures are shifted across midline

Subdural Hematoma (SDH) (Fig. 85.4)

SDH can be acute, subacute or chronic. Acute subdural hematoma is associated with poor outcome and is clinically characterized by sever depression of level of consciousness with focal deficit and cerebral injury.

Subacute subdural hematoma presents as progressive deterioration of consciousness and/or neurological function, associated with good outcome with appropriate and timely neurosurgical intervention.

Chronic subdural hematoma is the most common entity in pediatric traumatology, and is amenable to surgical treatment.

Intracerebral Hematoma and Contusions (Fig. 85.5)

These have variable and multiple presentations ranging from perfectly normal to mildly depressed level of consciousness, to severe neurological deficit, seizures and coma. They may or may not require surgical intervention, may or may not respond to surgical management depending upon extent and nature of damage.

Diffuse Brain Injury

Depending upon severity of impact, head injury could lead to minor concussion or diffuse axonal

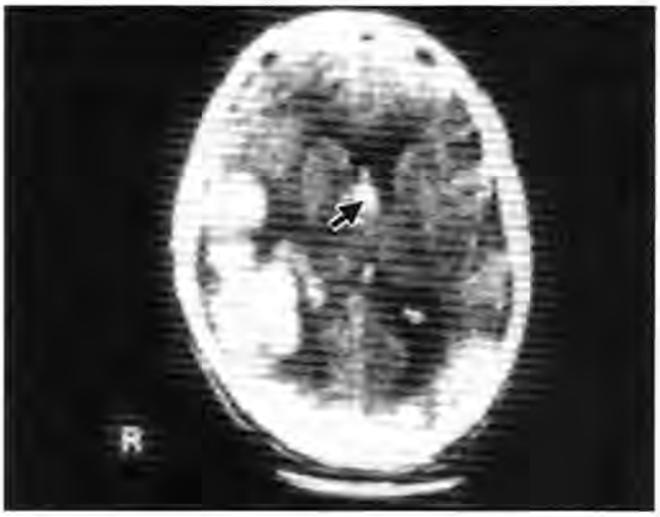


Fig. 85.5: Acute intracerebral hematoma—CT scan of brain demonstrating hyperdense mass in right parietotemporal area large acute intracerebral hematoma has shifted lateral ventricle toward midline. Blood is visualized within ventricular system (black arrow)

injury. A concussion is temporary loss of neurological function immediately after trauma with no radiological findings and associated with complete recovery. While diffuse axonal injury is usually due to shearing movements of the brain during acceleration deceleration injuries, it is almost always associated with poor outcome. Patient with poor neurological status whose clinical status does not correlate with CT scan findings should be subjected to MRI which usually will reveal lesion in corpus-callosum, rostral part of pons or in the internal capsule.

Other Injuries

Some of the other injuries commonly seen are CSF leak, growing fracture of skull or cerebral vascular injury.

Radiological Investigations

1. *Skull X-ray:* Lateral view and AP view of skull should be taken. It can reveal fracture, diastasis and other bony abnormalities. If a CT scan is easily available X-ray skull can be avoided as with a good CT all the relevant information obtained X-ray can be obtained with bone windows detecting any fractures.
2. *CT Scan:* CT[20-22] is the investigation of choice. It reveals boney injury, hematoma (appears hyperdense when compared to brain parenchyma), evidence of cerebral edema (hypodense compared to normal brain parenchyma and isodense compared to CSF) or mass effect (midline shift). CT is necessary for operative planning.
3. *MRI (Magnetic resonance imaging) Scan*: MRI had no role in acute management of a patient with head injury. It can be used in cases of diffuse axonal injury and in follow-up for prognostication. Some time a small lesion in vital areas of brain may not be seen on CT but seen on MRI. MRI is usually reserved for later detailed evaluation after acute problem has been addressed.
4. *Cervical Spine (Lateral View):* A lateral view of the cervical spine is obtained in the emergency room to rule out cervical bony injury or dislocation. This must be followed by full cervical spine series with anteroposterior and oblique views to rule out any fracture or dislocation. Cervical spine collar should be kept on until a fracture or dislocation of the cervical spine has been ruled out.

Neurosurgical Management

Neurosurgical management includes operative removal of extradural (epidural) hematoma or subdural hematomas as soon as possible after the diagnosis is made. ICP monitor needs to be placed in most cases for ICP and CPP monitoring and further management in the pediatric intensive care unit (PICU) (see chapter on Monitoring).

NONSURGICAL MANAGEMENT

Management in the PICU (Figs 85.6, 85.7 and Flow chart 85.1)

The basic aim is to minimize the primary injury and prevent secondary insult to the brain. Treatment remains supportive. As discussed in pathogenesis the key to management of a head injured patient with cerebral edema or diffuse axonal injury is to maintain cerebral perfusion pressure by control of ICP and hemodynamic status.

Primary cerebral injury is due to trauma per se, accumulation of blood clot and tissue damage leading to decreased cerebral blood flow, increased

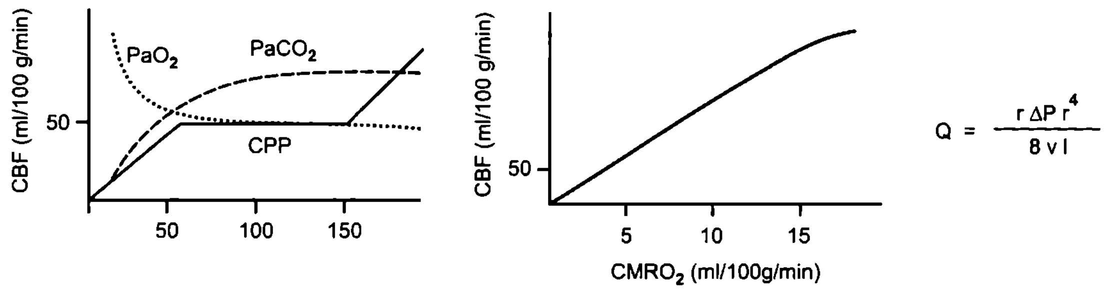


Fig. 85.6: Influence of PaO_2, $PaCO_2$, cerebral perfusion pressure, cerebral metabolic rate for oxygen ($CMRO_2$), and \ on cerebral blood flow (CBF) in normal brain. Q, flow; ΔP–change in pressure; r–vessel radius; v–viscosity; l–vesse

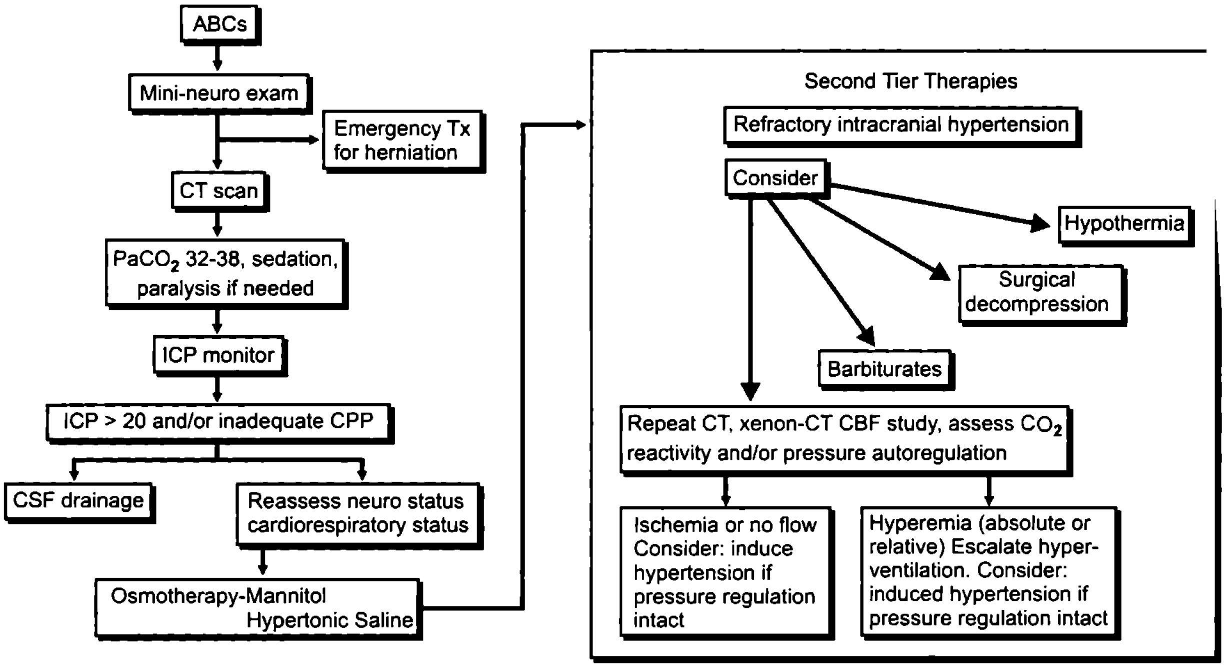

ABCs
Mini-neuro exam
Emergency Tx for herniation
CT scan
PaCO2 32-38, sedation, paralysis if needed
ICP monitor
ICP > 20 and/or inadequate CPP
CSF drainage
Reassess neuro status cardiorespiratory status
Osmotherapy-Mannitol Hypertonic Saline
Second Tier Therapies
Refractory intracranial hypertension
Consider
Hypothermia
Surgical decompression
Barbiturates
Repeat CT, xenon-CT CBF study, assess CO2 reactivity and/or pressure autoregulation
Ischemia or no flow Consider: induce hypertension if pressure regulation intact
Hyperemia (absolute or relative) Escalate hyper-ventilation. Consider: induced hypertension if pressure regulation intact

Fig. 85.7: An intracranial pressure-directed algorithm for the management of patient with severe head injury. Tx-treatm CT-computed tomography, ICP-intracranial pressure, CPP-cerebral perfusion pressure, CSF-cerebrospinal fluid. Cl cerebral blood flow

cerebral blood volume, increased intracranial pressure and decreased cerebral perfusion pressure.[23,24]

Secondary injury is mainly due to failure of autoregulation and biochemical changes, which lead to cerebral edema (vasogenic, cytotoxic, hydrostatic or osmotic).

Tissue damage is mainly due to direct injury or apoptosis changes.

Seizure Control

Midazolam may be used to control seizures patients with status epilepticus. Propofol Thiopentone may also be used, however hypotensi associated with the use of these agents should treated with fluid therapy.

Phenytoin should be initiated in patients wi post-traumatic seizures, although use of prophylac phenytoin in all head injured children is not supported by clinical evidence. In patients who are sedated and muscle relaxed, EEG should be monitored and nonconvulsive seizures should be controlled to reduce the cerebral oxygen consumption.

Management of Intracranial Hypertension and Cerebral Perfusion Pressure (CPP)

Intracranial hypertension is defined as ICP > 20 mmHg for > 5 min. Recommendations for adults include maintaining an ICP of less than 20 mmHg and perfusion pressure (CPP) of > 60 mmHg. These may be applicable for older children. Although no normal data is available through clinical evidence, in infants with severe traumatic brain injury it would be logical to suggest targeting for an ICP of < 15 mmHg and a CPP of > 45 to 50 mmHg. Careful use of inotropic agents such as dopamine may be necessary to maintain these parameters, however induced hypertension with phenylephrine is not recom-mended since cerebral autoregulation is lost and further increase in cerebral blood flow may exacerbate edema formation by hydrostatic effect.[25, 26] CSF drainage by venticulostomy has been shown to be as effective as mannitol therapy in reducing ICP.[27]

Hypoxia and hypotension at any point of management is associated with poor outcome, should, therefore be avoided or promptly treated.

Mechanical Ventilation

In all children with Child Coma Score is less than 8, intubation and mechanical ventilation is indicated, head should be kept in midline and 30 degrees elevated position.[28] Arterial blood gases should be monitored to maintain PCO2 levels between 31 to 32 rather than 26 to 27 mmHg for better outcome 6 months after trauma.[29] Hypercarbia must be avoided. Positive endexpiratory pressures (PEEP) in the range of 4 to 5 cm of H_2O are harmless as far as ICP is concerned and should be used to prevent atelectasis. For impending herniation mannitol and transient hyperventilation to achieve $paCO_2$ 25 mm to 30 mmHg is beneficial. Midline position with slight head elevation to 45 degrees is helpful during mechanical ventilation to achieve reduction of ICP.

Sedation and Muscle Relaxation

Sedation and muscle relaxation is recommended for adequate control of ICP. Fentanyl, midazolam and vecuronium infusion is a good combination as long as hypotension is avoided. Subject to availability, pentobarbitone, phenobarbitone, propofol may be used. Intermittent thio-pentone and Intravenous lidocaine is recommended to blunt raised ICP response while suctioning the endotracheal tube. Alternatively instillation of lidocaine in the endotracheal tube may be as effective.

Fluid Therapy

Initial resuscitation should be done with normal saline or ringers lactate solution to support hemodynamic status in a hypotensive patient. A central line should be placed to guide fluid therapy by central venous pressure monitoring. Glucose should be maintained at normal level. Hypoglycemia should be avoided in infants and neonates. More commonly, due to stress of the head injury, serum glucose is high, glucose containing fluids should be avoided initially. Ringers lactate or half normal saline may be used. Hypertonic saline has been used by some centers in presence of hyponatremia due to cerebral salt wasting syndrome. Hypertonic saline used for reducing refractory ICP, has however not been shown to affect survival in clinical studies.[30]

If hyponatremia is due to SIADH (syndrome of inappropriate antidiuretic hormone secretion) fluid restriction may be required. Blood and plasma are used as guided by the hematocrit and coagulation profile.

Mannitol

Mannitol can reduce ICP by two machanisms. Reduction of viscosity which is transient, and dependent upon autoregulation being intact. More potent action, however is by its osmotic effect.

Mannitol in dosages of 0.5 to 1 gm/kg may be used intravenously at 6 hourly interval with monitoring of serum osmolality (to be kept under 320). Mannitol should not be used if serum osmolality is > 330, patient is hypotensive, patients with renal failure. Rapid pushes of mannitol can transiently increase ICP by causing transient systemic hypertension, therefore should be avoided. Mannitol has a theoretical risk of enlarging a hematoma by rapid shrinkage of brain and tearing of bridging veins. Therefore a CT may be necessary to rule out a hematoma before mannitol therapy is initiated.

Hypertonic saline 3 percent saline 2-3 ml/kg can be used to maintain serum sodium in the range of 150-160.

Induced Hypothermia

Prevention of iatrogenic hyperthermia and prompt treatment for fever is very important to keep cerebral metabolic oxygen requirements down.

In patients with refractory ICP induced hypothermia may be used as a last resort, however clinical studies have shown this to be of no benefit.

Steroids

No clinical evidence to use in cerebral edema due to head injury. Steroid use should be reserved for patients with brain tumors.

Decompressive craniectomy: In refractory increased ICP inspite of all medical measures, as a last resort decompressive craniectomy should be tried.

Nutrition

Early institution of enteral feeds is recommended if there is no associated intraabdominal injury to major organs such as liver, spleen, or duodenal hematoma (see chapter on Nutrition in Critically Ill Children).

Rehabilitation

Tracheostomy may be indicated in patients in prolonged comatose state who cannot protect their airway or require long term ventilation.

Once patient is recovered from acute injury in the PICU, early physical therapy for prevention of deep vein thrombosis and prevention of contractures may be necessary. Arm, leg-hand and feet splints should be used as indicated.

Complication and Sequelae of Head Injury

Various sequelae can be seen as follows:

Early

- Transient cortical blindness
- Seizures
- Cranial Nerve palsy
- Diabetes insipidus
- Syndrome of inappropriate secretion of ADH
- Cortical venous occlusion
- Hemiparesis.

Late

- Post-traumatic epilepsy
- Post-traumatic aneurysm
- Meningitis
- Hydrocephalus
- Memory loss
- Disability
- Muscle cotractures

Outcome after pediatric head injury[9]

Child outcome score has been described based on various parameters such as neurological and cognitive deficit.

Child outcome score

1. Child Outcome Score Excellent recovery
2. Mod but nondisabling deficit
3. Either a secure motor or cognitive deficit
4. Vegetative
5. Death:
   1 and 2—Good outcome
   3 to 5—Poor outcome.

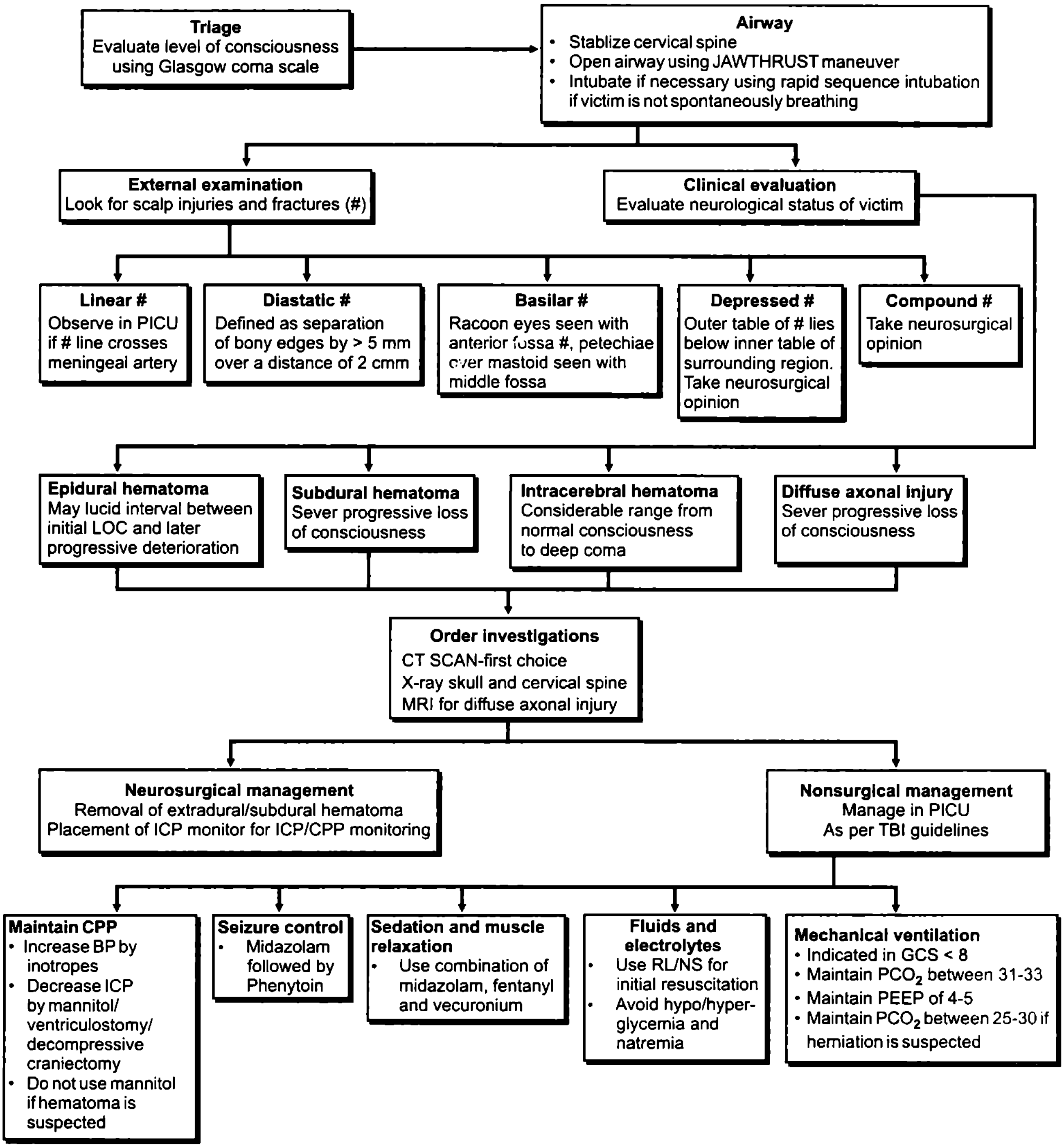
Indices of good outcome and poor outcome have already been described earlier in this chapter.

SUMMARY

Young children under 4 years of age have been shown to poor outcomes after severe head injury.

Severe traumatic brain injury remains a common problem with significant morbidity and mortality. A proper medical management needs an organized team approach ranging from prehospital care, emergency room and pediatric intensive care management. Prompt detection of mass lesions

Flow chart 85.1: Pediatric head trauma


Triage
Evaluate level of consciousness using Glasgow coma scale
Airway
• Stablize cervical spine
• Open airway using JAWTHRUST maneuver
• Intubate if necessary using rapid sequence intubation if victim is not spontaneously breathing
External examination
Look for scalp injuries and fractures (#)
Clinical evaluation
Evaluate neurological status of victim
Linear #
Observe in PICU if # line crosses meningeal artery
Diastatic #
Defined as separation of bony edges by > 5 mm over a distance of 2 cmm
Basilar #
Racoon eyes seen with anterior fossa #, petechiae over mastoid seen with middle fossa
Depressed #
Outer table of # lies below inner table of surrounding region. Take neurosurgical opinion
Compound #
Take neurosurgical opinion
Epidural hematoma
May lucid interval between initial LOC and later progressive deterioration
Subdural hematoma
Sever progressive loss of consciousness
Intracerebral hematoma
Considerable range from normal consciousness to deep coma
Diffuse axonal injury
Sever progressive loss of consciousness
Order investigations
CT SCAN-first choice
X-ray skull and cervical spine
MRI for diffuse axonal injury
Neurosurgical management
Removal of extradural/subdural hematoma
Placement of ICP monitor for ICP/CPP monitoring
Nonsurgical management
Manage in PICU
As per TBI guidelines
Maintain CPP
• Increase BP by inotropes
• Decrease ICP by mannitol/ ventriculostomy/ decompressive craniectomy
• Do not use mannitol if hematoma is suspected
Seizure control
• Midazolam followed by Phenytoin
Sedation and muscle relaxation
• Use combination of midazolam, fentanyl and vecuronium
Fluids and electrolytes
• Use RL/NS for initial resuscitation
• Avoid hypo/hyper-glycemia and natremia
Mechanical ventilation
• Indicated in GCS < 8
• Maintain PCO_2 between 31-33
• Maintain PEEP of 4-5
• Maintain PCO_2 between 25-30 if herniation is suspected

(hematomas) and neurosurgical intervention is very important. In nonneurosurgical patients with cerebral edema, control of ICP and cerebral perfusion pressure by ICP monitoring, mechanical ventilation, hemodynamic support, mannitol and judicious use of fluids and blood products have been helpful in successful management of these children.

Use of helmets, seat belts, infant seats and restraints are probably most important measures to prevent severe injuries in case of an accident. In addition, child and adult education regarding road safety, following traffic signals, care during road crossing can go a long way. See Appendix for traumatic brain injury guidelines.

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APPENDIX

GUIDELINES FOR ACUTE MEDICAL MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY IN INFANTS AND CHILDREN[1]

Guidelines for acute medical management of severe traumatic brain injury in infants, children and adolescents[1] were published on June 6, 2003 as special supplements to Pediatric critical care medicine, Critical care medicine and the journal of trauma, ensuring a multidisciplinary audience of more than 30,000 speciality physicians. According to brain injury association of America, more than 1 million children in the US sustain brain injuries each year, of whom 250,000 are admitted to hospitals, 7,000 die, and 30,000 are permanently disabled. Indian statistics though not available should be comparable at the least, following is a summary of available evidence in the literature. This information could be used to apply to care of head injuries in infants and children in the Indian scenario.

Evidence Highlights

1. Pediatric patients with traumatic brain injury should be treated in a pediatric trauma center or, failing that, a tertiary care hospital with pediatric trauma care capability.
2. Hypoxia must be treated appropriately; however, there is no evidence to support endotracheal intubation versus bag-mask ventilation during transfer to the hospital.
3. Prophylactic treatment with mannitol or mild hyperventilation is usually unnecessary but should be used in patients with evidence of cerebral herniation or worsening neurological function.
4. Intracranial pressure monitoring is indicated for children with a Glasgow coma score of less than 8, but it may also be employed for children in whom serial neurological examination is not feasible.
5. Treatment for increased intracranial pressure should be initiated when the pressure rises more than 20-25 mmHg.
6. The sensitivity of ventricular catheters, external guage transducers, or catheter tip pressure transducers in monitoring intracranial pressure appears equal.
   Subarachnoid, subdural, epidural, and externally placed monitors are less accurate.
7. Cerebral perfusion pressure should be maintained at more than 40 mm Hg. Further research is needed to determine an optimal cerebral perfusion pressure range.
8. The routine use of sedation and neuromuscular blockade in severe pediatric traumatic brain injury is not supported by scientific evidence. Coughing and bucking on the tube and suctioning maneuvers leading to increased intracranial pressure may necessitate their use, in practice.
9. Cerebrospinal fluid drainage via ventriculostomy is a first line option for refractory elevated intracranial pressure; lumbar drainage may be added in patients with open cisterns on imaging and without major mass lesions or midline shift.
10. Mannitol or hypertonic saline are both acceptable agents for lowering intracranial pressure.
11. Hyperventilation should only be used as a second line method to reduce refractory intracranial pressure. In this setting, the $PaCO_2$ should be kept at 25-30 mmHg.
12. High dose barbiturates may also be employed in the treatment of refractory increased intracranial pressure. Patients receiving this therapy require extremely close monitoring for hypotension.
13. Hyperthermia has been postulated to increase secondary mechanisms of brain injury in adults. Therefore, hyperthermia should be avoided in younger patients. Hypothermia on the other hand, may be beneficial, and when intracranial hypertension is refractory, the authors recommend that it be considered, despite lack of evidence.
14. Decompression craniectomy may also be considered to improve refractory intracranial hypertension. Surgical interventions may be more successful in patients with reversible brain insults.
15. There is no evidence to recommend steroid therapy in children with traumatic brain injury.
16. Although research had not directly addressed outcomes in pediatric patients with traumatic brain injury, nutritional support should be strongly considered with a goal of 130 to 160 percent of resting metabolic expenditure.
17. Prophylactic antiepileptic medications are not recommended.

CONCLUSION

1. Prompt recognition and transfer of pediatric victims of traumatic brain injury is paramount to good outcomes.
2. Intracranial pressure should be monitored and treated if > 20 mm Hg in children with severe brain injury.
3. Mannitol, hypertonic saline, ventricular drainage, hyperventilation, barbiturates and hypothermia should be considered in refractory intracranial hypertension.
4. Steroids and prophylactic antiepileptics have no role in traumatic brain injury in children.

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CHAPTER

86

Coma: Encephalitis and Cerebral Malaria

Krishan Chugh, Dhiren Gupta

A child presenting with coma is one of the most difficult diagnostic and management problems that may be encountered by a pediatrician. The gravity of the situation, the need to avoid further neurological damage, the wide range of possible causes call for a calm orderly approach to the problems at hand. Regardless of the etiology, initial management includes immediate attention to the ABCs in order to sustain life and prevent loss of brain function.

Definitions

Coma

Coma or altered mental status implies a disorder of consciousness, it may be applied to a state or continuum of worsening consciousness from being fully alert and responsive to deep unresponsive coma.

Stupor

Defined as severely impaired arousal, with some responsiveness to vigorous external stimuli.

Obtundation

Mild to moderate reduction in alertness with reduced awareness/responsiveness.

Delirium

State of confusion with periods of agitation, irritability, hallucination.

Confusion

It is impaired alertness or responsiveness.

Pathophysiology

Comatose state is indicative of diffuse impairment of cerebral functions, failure of brain stem activating functions or both. This may be caused by supratentorial lesions affecting deep diencephalic structures, sub-tentorial lesions affecting the brain stem or metabolic lesions diffusely affecting brain stem function.

Etiology

The etiologic possibilities of altered mental status are diverse.

1. Sepsis:
   - Gram-negative,
   - Enteric fever,
   - Cerebral malaria
   - Encephalitis/meningitis (Viral, Bacterial, Tubercular)
   - Hemorrhagic shock with encephalopathy
2. Drug toxicity
3. Malignant hyperthermia
4. Thyroid storm.
5. Porphyria
6. Trauma
7. Vascular (Intracranial hemorrhage/Infarction)
8. Epilepsy
9. Hypertensive encephalopathy:
   - Tumors, other malignancies
   - Hypoxic-ischemic encephalopathy.

Evaluation of a Child in Coma (Flow chart 86.1)

Prime Considerations

- Assess and optimize airway, breathing and circulation for adequate cerebral perfusion.

- Obtain an immediate bedside blood glucose level and correct if low.
- Brief relevant history regarding fever, trauma, congenital heart disease and ingestion of drug.

Secondary Considerations
(Tables 86.1 to 86.3)

A complete neurological examination is necessary. These may give valuable information about the level of the lesion in the brain, nature of involvement and direction of progression of the disease process. These are:

- General examination
- The level of consciousness
- Pattern of respiration
- Size and reactivity of the pupils
- Motor responses.

Table 86.1: Neurological examination

State of consciousness and alertness
Oriented vs confused
Spontaneous and stimulated interactions with environment
Eye opening, best motor and best verbal responses
Attention span
Developmental evaluation
Language
Gross motor
Fine motor
Social
Mental status examination
Language: speech, comprehension, naming, repeating, writing, reading
Drawing
Math
Praxis
Memory
Fund of knowledge
Reasoning: similarities, proverbs
Judgment and humor
Mood
Hallucinations, delusions, obsessions
Cranial nerves
I: Smell
II: Visual acuity, visual fields, fundi: dises, vessels, macula background
III, IV, VI: Extraocular movement: pupillary reaction to light: direct and consensual, nystagmus, ptosis, strabismus.
V: Masseters, pterygoids, facial sensation, corneals
VII: Orbicularis oris, oculi, frontalis: taste, anterior two thirds of tongue; stapedius, loss leads to hyperacusis

Contd...

Contd...

VIII: Hearing, vestibular responses
IX: Elevation of palate; gag reflex
X: Swallowing, movement of vocal cords
XI: Sternocleidomastoid, trapezius function
XII: Tongue movement, fasciculations
Motor
Strength: atrophy, fasciculations, weakness
Tone: passive, active, posture
Abnormal movements: tremor, chorea, athetosis, tics, myoclonus, seizures
Co-ordination: finger to nose, rapid alternating movements, heel to shin, ocular dysmetria, rebound
Gait: spontaneous, heel, toe, tandem, romberg reflexes
Tendon jerks: knee, ankle, biceps, triceps, brachioradialis, pectorals, finger flexors
Superficial: abdominal, cremasteric, anal, Babinski's
Infants: suck, root, step, place, Moro, grasp
Frontal release: snout, grasp, root, suck, glabellar reflex
Sensory
Touch, pin, temperature
Vibration, joint position sense, deep pressure
Double simultaneous stimulation, graphesthesia
Stereognosis, two-point discrimination, touch, localization

Table 86.2: Localization of upper motor neuron lesions

Signs	Localization
Aphasia Cortical sensory loss (graphesthesia, stereognosis, two-point discrimination) Gaze preference Unilaterally diminished opticokinetic nystagmus Visual field deficit	Cerebrum
Equal paralysis of face, arm, and leg Motor loss without sensory symptoms Motor loss with dense hemisensory deficit	Internal capsule
Hemiplegia with contralateral third nerve palsy (Weber)	Midbrain
Hemiplegia with contralateral sixth or seventh nerve palsy (Millard-Gubler)	Pons
Spastic weakness, difficulty swallowing and phonating, in co-ordination	Medulla
Weakness of one leg with contralateral loss of pain and temperature sensibility (Brown-Sequard)	Spinal cord
Paraplegia, sensory level, bowel and bladder dysfunction	Spinal cord

Table 86.3: Different levels of lesions and clinical findings

Site of lesion	*Brain stem intact*	*Uncal*	*Diencephalic*	*Midbrain*	*Pontine*	*Medullary*
1. Respiration	Normal		Cheyne- stokes; hyperpnea alternates with apnea-	Central neurogenic hyperventilation; fast and deep	Ataxic-irregularly irregular	Gasps
2. Response to supraorbital, nail bed pain		Hemiparesis	Flexion	Extension	None	None
3. Posture	Normal	Hemi-paresis	Decorticate	Decerebrate		Flaccid
4. Tone DTR's	Normal	Unilateral pyramidal	Bilateral pyramidal		Flaccid/extensor plantars	Flaccid
5. Oculo-cephalic*	Saccades present		Full deviation,	Minimal deviation	No movement	
6. Oculovestibular†	Nystagmus		Full deviation, eyes towards	Minimal deviation of eyes	No movement	
7. Pupil size and reaction bright torch	Normal, brisk	Unilaterally dilated, not reacting-	Small, pinpoint, reacting	Midpoint, fixed to light	Pinpoint, reactive but difficult to appreciate	Bilaterally dilated, fixed (do not constrict with miotic agents)

**Oculocephalic-exclude cord injury and turn head side to side with intact brain stem eyes would look away from the side of head turning*
† Oculovestibular-exclude perforated ear drums,head in midline and 30° elevated,inject 20 ml ice cold water into ear canal,with intact brain stem eyes would look towards the side of instillation.

Table 86.4: General examination

Features	*Possibility*
• Nose, ear bleeding, scalp bruising or hematoma	Head injury
• Inconsistent history, retinal hemorrhage	Non-accidental injury
• Fever, seizures, meningeal signs	CNS infections
• Focal neurological signs	Focal intracerebral pathology, e.g. abscess, granuloma and tumor
• Focal seizures	
• Papilledema	
• Asymmetric pupils	
• Shunted hydrocephalus	Blocked shunt
• Renal disease	Hypertensive encephalopathy
• Recurrent vomiting, abnormal body odor, hyperventilation, skin rash	Neuro-metabolic
• Diarrhea and dehydration	Fluid and electrolytes imbalance, venous thrombosis

General Examination (Table 86.4)

A thorough general examination can provide some clue regarding etiology. Inspection of scalp, skin for evidence of rash, mosquito bite, bleeding, pigmentation, jaundice or neurocutaneous markers. Other than pulse rate, temperature, blood pressure, look for abnormal smell, cardiac murmur, or evidence of hepatosplenomegaly (Table 86.4).

Level of Consciousness

The most useful is the *Glasgow Coma Score* (GCS), which was originally used to predict the outcome after head injury in adults. The *modified GCS* is applicable to younger patients and is the most frequently used general means of neurological assessment.

The Glasgow Coma Score

Eye opening response

< 5 years	*>5 years*	*Score*
Spontaneous	Spontaneous	4
To speech	To speech	3
To pain	To pain	2
None	None	1
Verbal response		
Alert, coos, words—normal	Oriented	5
Irritable cry	Confused	4
Cries to pain	Inappropriate words	3

Contd...

Contd...

Moans to pain	Incomprehensible sounds	2
No response to pain	None	1
Motor response		
Normal spontaneous movements	Obeys commands	6
Localizes (> 9 months)	Localizes to supraorbital stimulus	5
Withdraws	Withdraws	4
Abnormal flexion (decorticate posturing)	Abnormal flexion (decorticate posturing)	3
Abnormal extension (decerebrate response)	Abnormal extension (decerebrate response)	2
None	None	1

Anatomical and Etiological Localization

Supratentorial destructive or mass lesions

1. Initial signs focal; combination of focal motor and cranial nerve deficits help in determining probable site of lesion.
2. Rostral-caudal progression

Infratentorial destructive or mass lesions

1. Preceding brain stem dysfunction
2. Sudden onset of coma
3. Cranial nerve palsies.
4. Early respiratory disturbances.

Toxic, metabolic or infectious disease

1. Confusion or stupor precedes motor signs.
2. Motor signs symmetric
3. Pupillary reactions preserved till late.
4. Asterixis, myoclonus, tremor or seizures.
5. Hyper/hypoventilation.

Respiratory Pattern

The control of respiration is governed by centers located in the brain stem (lower pons and medulla) and modulated by forebrain cortical centers. Respiratory pattern abnormalities signify either metabolic derangements or neurologic insult.

Several characteristic respiratory patterns exist:

- *Cheyne-Stokes respiration:* This is a pattern of periodic breathing where *hyperpnea* alternates with apnoea. Cheyne-Stokes respiration results from deep hemispheric or diencephalic dysfunction and may also be seen in children with metabolic abnormalities.
- *Central neurogenic hyperventilation:* Sustained regular, rapid and deep respiration. May be seen in children with brain stem dysfunction.
- *Apneustic breathing:* This pattern of breathing is characterized by inspiratory pauses lasting 2-3 seconds often alternating with end-expiratory pauses. Apneustic breathing is characteristic of pontine infarction and anoxic encephalopathy.

Pupillary Size and Reactivity

Pupillary reactions are controlled by a balance between the sympathetic and parasympathetic nervous system. As brain stem centers controlling consciousness are anatomically adjacent to those controlling pupils, pupillary changes are a valuable guide to the presence and location of brain lesions. Additionally, metabolic disturbances affect pupillary pathways late. Consequently, the presence or absence of the pupillary reaction to light is one of the single most important differentiating features to distinguish between structural and metabolic disorders.

Central Nervous System and Motor Examination

Assessment of muscle strength, tone and tendon reflexes should be done for normality and symmetry. The ability of the patient to localize stimuli as well as the presence or absence of abnormal posturing helps in the assessment of severity of the neurological derangement.

Decorticate posturing with flexion of the upper extremities and extension of the lower extremities suggests involvement of the cerebral cortex and preservation of brain stem function.

Decerebrate posturing with rigid extension of the arms and legs is indicative of cortical and brainstem damage.

The *flaccid patient* with no response to painful stimuli has the gravest prognosis with injury sustained to deep brain stem lesions.

Recurrent coma: Consider the following possibilities:

- Epilepsy
- Hypoglycemia
- Increased intracranial pressure (recurrent)
- Neuro-metabolic disorders
- Mitochondrial disorders
- Migraine
- Substance abuse
- Endocrinal (Hashimoto-thyroiditis)

Laboratory Evaluation

Laboratory evaluation of a patient in coma should include the following:

White blood count, coagulation screen, blood smear for malaria and detection of malarial antigen, arterial blood gas, blood glucose, serum electrolytes, calcium, magnesium, urine for sugar, ketones, pH, infection screen, chest X-ray.

Above investigations to be done in all patients and some specific investigations to be done when clinically indicated.

Serum ammonia, lactate, pyruvate in suspected metabolic disorders

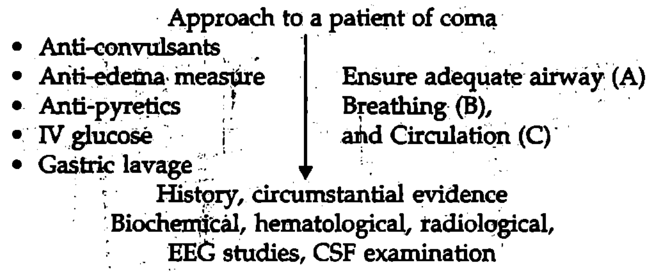
Liver, renal function tests

Lumbar puncture; To be done-If meningitis suspected. Contraindicated if- Overt raised ICP, herniation syndromes, GCS<8, focal neurodeficits, bleeding diathesis/local site infection.

Neuroimaging-Urgent CT head if trauma or clinical suspicion of child abuse, focal neurodeficits, diffuse encephalopathy but sepsis and metabolic screens negative. Initial normal CT does not rule out an evolving lesion of an infection or metabolic disorder. In herpes simplex encephalitis (HSE) CT head is abnormal in around 50 percent of cases but may be normal l in 1st 4-5 days. Uni/bilateral hypodensities in frontotemporal areas with occasional hemorrhage are seen . MRI is abnormal in around 70-80 percent of HSE cases. Asymmetrical hyperintensities in T2WI are seen in orbital surface of frontal lobe, medial part of temporal lobe, insular cortex and cingulate gyrus; hemorrhage may also be seen. Meningeal and gyral enhancement may be present esp. in neonates and children. If possibility of inborn error of metabolism then MRI brain may give clues to diagnosis e.g. basal ganglia signal changes in organic acidemias and mitochondrial encephalopathies, white matter signal changes in urea cycle defect and maple syrup urine disease.

EEG-Serial EEG's are more useful than isolated. Relatively specific in herpes simplex encephalitis. It helps in detection of non convulsive status epilepticus as a cause of coma. Plenty of beta activity may occur with sedative drug overdose. Metabolic encephalopathy like hepatic show triphasic waves. Assist in prognosticating regarding later neurological outcome. Those with low amplitude EEG/ electrocerebral silence unlikely to do well. Comatose children with reactive electroencephalographic patterns have better clinical outcome in terms of morbidity and mortality.

Management


Approach to a patient of coma
• Anti-convulsants
• Anti-edema measure
• Anti-pyretics
• IV glucose
• Gastric lavage
Ensure adequate airway (A)
Breathing (B),
and Circulation (C)
History, circumstantial evidence
Biochemical, hematological, radiological,
EEG studies, CSF examination

For management we can further divide coma in three main categories.

- Specific cause for coma found.
- Cause strongly suspected
- Cause not found.

Supportive measures are required for all 3 categories.

Airway and Breathing

- Open airway (use only jaw thrust if cervical spine injuries suspected)
- Oral airways may be used only if atraumatic insertion possible
- Early intubation using Rapid Sequence Intubation with full stomach precautions
- Indications for intubation in the comatose patient
  - GCS < 8
  - Inability to maintain airway patency or protection
  - Impaired oxygenation or ventilation

Cardiovascular Stabilization

Assess circulatory status. If in shock, treat along standard guidelines with boluses of isotonic fluid and pressors as indicated.

Management of Raised ICP

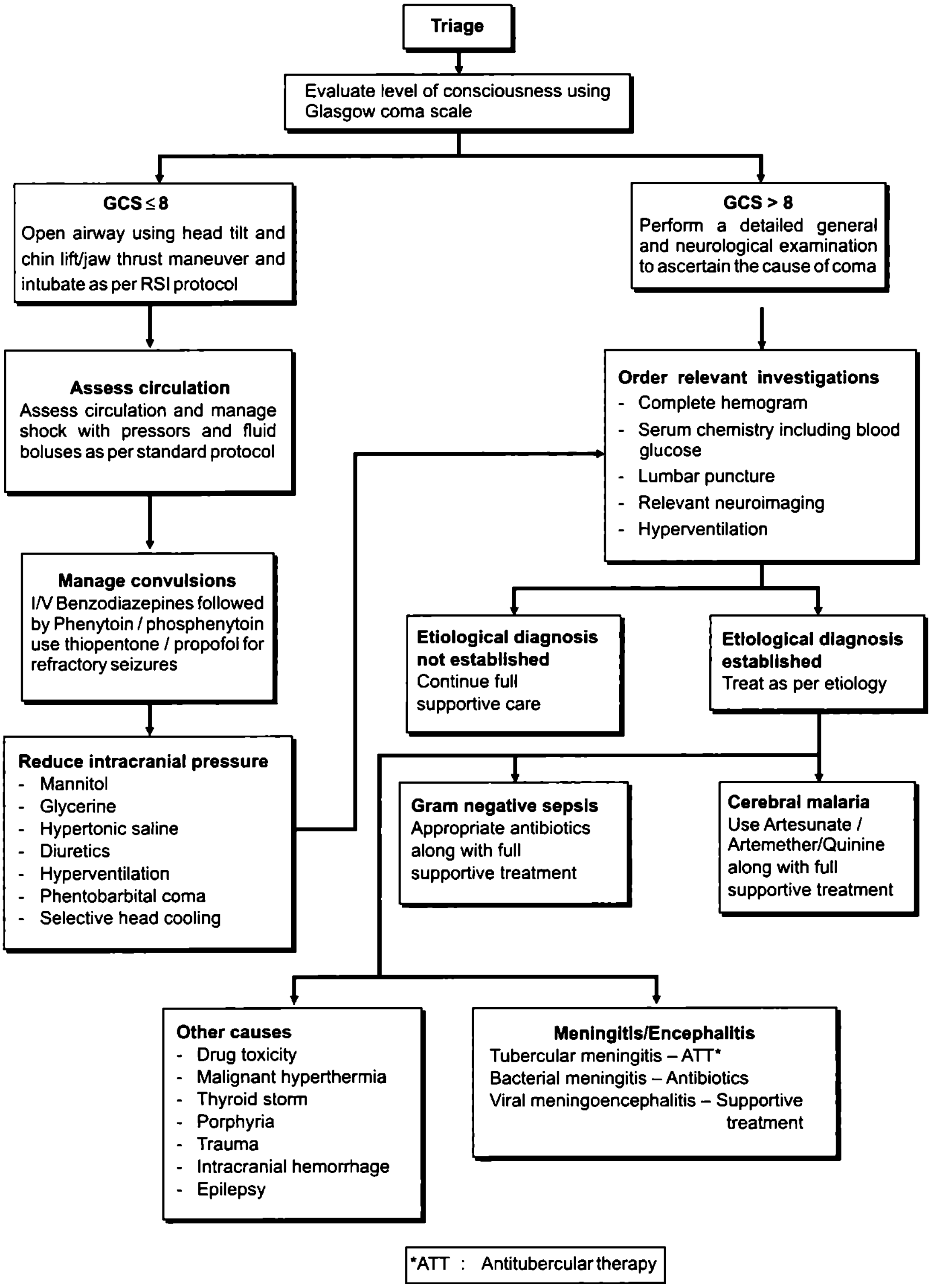
Seizure Control

IV benzodiazepines followed by phenytoin / fosphenytoin

Benzodiazepine drip: Midazolam or Diazepam depending on the availability

Refractory status epilepticus-Thiopentone, propofol

Flow chart 86.1: Approach to comatose child


Triage
Evaluate level of consciousness using Glasgow coma scale
GCS ≤ 8
Open airway using head tilt and chin lift/jaw thrust maneuver and intubate as per RSI protocol
GCS > 8
Perform a detailed general and neurological examination to ascertain the cause of coma
Assess circulation
Assess circulation and manage shock with pressors and fluid boluses as per standard protocol
Order relevant investigations
- Complete hemogram
- Serum chemistry including blood glucose
- Lumbar puncture
- Relevant neuroimaging
- Hyperventilation
Manage convulsions
I/V Benzodiazepines followed by Phenytoin / phosphenytoin use thiopentone / propofol for refractory seizures
Etiological diagnosis not established
Continue full supportive care
Etiological diagnosis established
Treat as per etiology
Reduce intracranial pressure
- Mannitol
- Glycerine
- Hypertonic saline
- Diuretics
- Hyperventilation
- Phentobarbital coma
- Selective head cooling
Gram negative sepsis
Appropriate antibiotics along with full supportive treatment
Cerebral malaria
Use Artesunate / Artemether/Quinine along with full supportive treatment
Other causes
- Drug toxicity
- Malignant hyperthermia
- Thyroid storm
- Porphyria
- Trauma
- Intracranial hemorrhage
- Epilepsy
Meningitis/Encephalitis
Tubercular meningitis – ATT*
Bacterial meningitis – Antibiotics
Viral meningoencephalitis – Supportive treatment
*ATT : Antitubercular therapy

Avoid hyperthermia-antipyretics, shivering should be avoided

Head in midline and 30° elevated to promote cerebral venous drainage

Minimize painful stimuli: Adequate sedation and analgesia (benzodiazepines and opioids by infusion or frequent boluses)

Ensure adequate intravascular volume (use of normal or N/2 saline with added glucose in full maintenance doses and with concomitant monitoring of arterial and central venous pressure) and correct shock with fluid and inotropes. Restriction of fluids was not associated with better outcome in randomized controlled trials. Decreased intravascular volume and CPP correlated with poor neurological outcome. If evidence of SIADH as evidenced hyponatremia with normal urine sodium, high CVP or weight gain is there only then fluid restriction may be required.

Rapid sequence intubation and using intravenous lignocaine prior to intubation.

Pharmacotherapy to Reduce Raised ICP

- Osmotic agents-mannitol, glycerol, hypertonic saline. Intravenous boluses when impending herniation or features of raised ICP. Mannitol (20%) is generally given 6 hourly for 8 doses. Monitoring of electrolytes, osmolality on prolonged use is required.
- Diuretics (frusemide)-may be used as adjunct to osmotic agents as they act synergistically in reducing ICP.
- Hyperventilation-acute hyper ventilation in impending herniation not to exceed 1 hour as hypocapnia induced vasoconstriction may be counterproductive by reducing cerebral perfusion.
- Pentobarbital coma-only if ICU set up and bedside EEG available for monitoring.
- Hypothermia (more evidence accumulating but not a standard modality).

Specific Treatment

Antibiotics in appropriate doses; Acyclovir-if focal seizures/deficits, with a suggestive CSF/EEG/CT scan. Pulse high dose steroids if imaging suggestive of acute disseminated encephalomyelitis.Quinine in suspected cerebral malaria (endemic area, significant pallor with heaptomegaly or retinal hemorrhages or suggestive laboratory investigations).

Antidotes-Atropine for organophosphates, naloxone for opioids, flumazenil for benzodiazepines.

Nursing Care of Comatose Child

Minimal handling, Care of eyes to prevent exposure keratitis, Frequent change of position to prevent pressure sores, pain control, gentle suctioning and avoid vigorous physiotherapy

Early nutrition: Institution of nasogastric feeds early in the illness is beneficial.

Prognosis

Mortality reported from all causes of COMA is 19-35 percent depending on cause, depth and duration of coma.

Survival is better with increasing GCS. Poor verbal score at discharge associated with poor IQ.

Outcome is better in traumatic than non traumatic coma, worse after hypoxic ischaemic insult/cardiac arrest. Survival better in patients with CNS infection as compared to those with toxic-metabolic causes and intracranial bleed.

If global ischemia has not occurred during the course of encephalopathy then the outcome is much better than what appears when child just off ventilator. Cortical blindness often recovers. Hemiparesis/mild extrapyramidal disorder do well. Dystonic/spastic quadriparesis fare worse. Cognition recovers sufficiently but behavioral problems are common.

Predictors of Poor Outcome

1. On Serial EEG's–low voltage activity is associated with poor prognosis.
2. CT-head showing widespread low density is suggestive of global ischemia associated with a poor outcome.
3. Evoked potentials—In anoxic coma: The abolition of SSEPs is related to a poor outcome (death or survival in a vegetative state), with a 100 percent specificity.

Management of Some Common Specific Causes

Cerebral Malaria

It is defined as a major cerebral event such as seizures or coma in a subject with *P. falciparum* infection (positive blood smear), who has no other obvious explanation for that complication. Mortality rate in cerebral malaria ranges between 15-50 percent. It should be suspected in children who have fever, altered sensorium and no other obvious diagnosis. The index of suspecian should be especially high in endemic regions. The comatose patient should be given meticulous nursing. Monitoring of the level of consciousness (using modified Glasgow coma scale), temperature, respiratory rate, blood pressure, and vital signs should be done as described. With specific therapy, most children regain consciousness on day 2 or 3 of illness. There is no role of drugs to reduce cerebral edema. Following drugs have been used without benefit:

Corticosteroids, Mannitol 20 percent, Urea, Pentoxiphyllin, Desferioxamine, AntiTNF antibody, Cyclosporin, Hyperbaric oxygen.

It is important to know if patient has falciparum malaria since these patients may deteriorate rapidly if treatment is delayed, even if they appear clinically stable. Falciparum infection should be suspected in any peripheral smear with >5 percent infected RBCs. Traditionally, thick smears are used for the detection of the parasites and for quantitating parasitemia; thin smears are used for species identification. It is more rewarding to obtain smears several times daily than choosing a specific time for obtaining the smear as the level of parasitemia varies from hour to hour, especially in *P. falciparum* infection. A diagnosis of malaria can only be excluded by obtaining negative blood smears on several successive days.

Staining with fluorescent dye like acridine orange stain may provide faster and easier diagnosis of malaria but species are difficult to identify. Other methods like dip stic antigen capture assay are simple, accurate and more useful when expert is not present to examine the slide. Their sensitivity ranges from 75 to 96 percent and specificity from 89-100 percent. A negative test virtually rules out malaria. Immunochromatographic test is a simple, accurate and inexpensive test. It can detect very low levels of parasitemia that may have been missed by inexperienced staff or poorly prepared films. PCR tests for malarial antigens in the blood or CSF are also available.

Specific Treatment of Malaria

Chemotherapy

Complicated/severe malaria (> 5% parasitemia and signs of either shock or end organ involvement) in India should be treated as malaria with drug resistance. Drug dosages are given in Table 86.5.

Role of Artemisinin Derivatives and Other Drug Combination in Malaria

WHO has recommended that Artemisinin is a safe and effective alternative to quinine for the treatment of severe malaria especially in areas where quinine resistance is suspected; and to improve efficiency of the drug and delay onset of resistance, artemisinin should always be used in combination with another effective antimalarial. As per Cochrane review artemisinin drugs are no worse than quinine in preventing death in severe or complicated malaria. No artemisinin derivative appears to be better than the others.

In Thailand, the efficacy of mefloquine has decreased considerably after several years of intensive use, but the combination of mefloquine and artesunate is more than 95 percent effective in multiresistant areas.

Studies evaluating the efficacy and tolerance of artesunate in combination with chloroquine, amodiaquine and sulfadoxine-pyrimethamine are under way in Africa and South America. Only one fixed combination that includes an artemisinin derivative for oral use is available: artemether-lumefantrine (an amino-alcohol related to halofantrine). For the moment, these combinations with artemisinin derivatives are costly.

Artemisinin derivatives should not be used in mono-therapy to treat uncomplicated malaria infections, if ever they are prescribed, they should be administred for at least seven days. Artemether and arteether are available in injectable form for the treatment of severe malaria.

Preparations and doses are given below (Table 86.6).

Table 86.5: Dosages of antimalarial therapy

Drugs	*Dosages and comments*
Quinine*	*If an infusion pump is available:* Quinine (base) 5.8 mg/kg loading dose [quinine dihydrochloride (salt) 7 mg/kg] intravenously by infusion pump over 30 minutes followed immediately by 8.3 mg base/kg [quinine dihydrochloride (salt) 10 mg/kg] diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 hours, repeated 8 hourly (maintenance dose) for up to 72 hours or until the patient can take orally thereafter quinine tablets to complete 7 days of treatment *Without an infusion pump* Quinine (base) 16.7 mg/kg loading dose [quinine dihydrochloride (salt) 20 mg/kg], by intravenous infusion over 4 hours, then 8.3 mg base/kg [quinine dihydrochloride (salt) 10 mg/kg] diluted in 10 mL/kg isotonic fluid by intravenous infusion over 4 hours, repeated 8 hourly (maintenance dose) for up to 72 hours or until the patient can take orally thereafter quinine tablets to complete 7 days of treatment. *PLUS (either concurrently with quinine or immediately after)*
Doxycycline	Pediatric dose 2 mg/kg (to a maximum of 100 mg) twice daily Contraindicated for age < 8 years. or
Pyrimethamine/ Sulfadoxine	*Children:* Less than 1 year, ¼ tablet; 1 to 3 years, ½ tablet; 4 to 8 years, 1 tablet; 9 to 14 years, 2 tablets; orally once on last day of quinine therapy. or
Clindamycin	10 mg/kg (loading dose) intravenously, followed by 5 mg/kg every 8 hours until blood is clear of asexual parasites (to be given when patient unable to take doxycycline, tetracycline or pyrimethamine/sulfadoxine). Loading dose should not be used if patient received quinine or mefloquine within the preceding 24 hours

Note: *All cases to switch to oral therapy as soon as possible.*

**When quinine is administered to a patient who has taken mefloquine or halofantrine in the previous 2 weeks, there is a risk of drug-induced cardiac arrhythmia; if possible, such patients should be monitored electrocardiographically. Approximately 5 percent or more of patients may fail treatment for falciparum malaria. Most patients fail within 1 month of treatment. To ensure that patients are cured, it is important to repeat a thick and thin blood film on day 7 and day 28 after therapy, and at any time when there is recurrence of symptoms.*

Table 86.6: Dosages of antimalarial therapy for resistant malaria

Drugs	*Dosages*
Artisunate	2 milligrams/kilogram (mg/kg) intravenously or intra-muscularly recommended initially, followed by 1 mg/kg every 12 hours until oral therapy possible; oral therapy should be continued for total treatment period of 7 days
Artemether	It is oil-soluble and is administered intramuscularly. 3.2 milligrams/kilogram initially, followed by 1.6 milli-grams/kilogram every 12 to 24 hours given for 3-5 days

Ancillary Treatment of Severe Malaria (Table 86.5)

Several ancillary treatments have been suggested for the treatment of severe malaria, but few have been objectively shown to improve outcome. Only antipyretics (acetaminophen) and anticonvulsants (prophylactic phenobarbital) have been supported by sufficient evidence to warrant their use. Vitamin A deficiency is common in persons in malaria endemic area. It may impair development of immunity against *P. falciparum* or exacerbate the disease. In children with cerebral malaria, whitening of the retina is a distinctive ocular fundus finding. It is associated with low serum vitamin A levels and may be due to acute vitamin A deficiency at the tissue level. Vitamin A supplementation may be effective strategy to lower morbidity due to *P. falciparum* in young children.

Deficiency of thiamine: Its deficiency is common in some parts of SE Asia and often complicates acute falciparum malaria among adults, particularly those with severe infection. It may contribute to CNS dysfunction.

Poor Prognostic Indicators in Cerebral Malaria

These are as follows: Impaired consciousness (deeper the coma, worse the prognosis), Repeated seizures ($\geq$ 3 in 24 h), Respiratory distress (rapid, deep, labored, stertorous breathing), Significant bleeding, Shock, Renal impairment (serum creatinine >3 mg/dl) (esp poor if combined with deep jaundice), Acidosis (plasma bicarbonate < 15 mmol/L), Jaundice (serum total bilirubin > 2.5 mg/dl) (esp poor if combined with renal failure), Hyperlactatemia (venous lactate > 45 mg/dl), Hypoglycemia (blood glucose < 40 mg/dl), Elevated aminotransferase levels (> 3x normal), Parasitemia (> 500,000 parasites/mm or > 10,000 mature trophozoites and schizonts/mm., and > 5 percent of neutrophils contain malaria pigment.

ENCEPHALITIS

As stressed previously, the first priority in the management of comatose patients is the preservation of vital functions. Assess the airway, breathing and circulation. Emergency management of intracranial hypertension is potentially life saving in all encephalopathies. Assessment of brain stem function is carried out with the possibility of central or uncal herniation in brain. Consequently, neurological assessment should focus on papillary responses, respiratory pattern, motor responses (response to pain, tone, abnormal posturing). Papilledema is very rarely seen in the acute setting, even if the intracranial pressure is very high. If evidence of raised ICT is present, institute immediate therapeutic measures. Other than general measures rule out bacterial infection by doing CSF examination. Among viral infections which can affect brain is herpes infection is an important one.

Herpes Encephalitis

It is the most common cause of sporadic viral encephalitis, with a predilection for the temporal lobes and a range of clinical presentations, from aseptic meningitis and fever to a severe rapidly progressive form involving altered consciousness. The most common early symptoms are headache and fever. Additional symptoms include intellectual impairment, aphasia, meningeal signs, seizures and paresthesias. Early treatment is crucial to a good outcome, with empiric acyclovir therapy initiated before a definitive diagnosis can be established. The virus cannot be cultured routinely from cerebrospinal fluid (CSF), although lymphocytic pleocytosis and elevations in protein concentration are observed. CSF viral cultures are positive for HSV in fewer than 5 percent of patients. Anti-HSV antibodies often do not appear until 1-3 weeks after symptom onset; therefore, antibody assay is helpful only in retrospective diagnosis. In some patients, a brain biopsy may be required for a definitive diagnosis.

EEG also can reveal focal temporal abnormalities, which are seen in 80 percent of patients; a normal EEG is believed to exclude the diagnosis. Periodic lateralized epileptiform discharges also support the diagnosis but are nonspecific. Historically, a brain biopsy provided a definitive diagnosis, but this procedure is not highly sensitive and can result in complications, including hemorrhage and edema at the biopsy site.

An RNA polymerase test of CSF obtains a more definitive diagnosis, since it is both sensitive and specific. In this test, 2 sets of oligonucleotide primers amplify gene products from HSV-1 and HSV-2.

Following DNA amplification, a Southern blot technique identifies the characteristic herpes simplex banding. The test is positive early in the disease and has a turnaround time of approximately 24 hours. This test is now considered the criterion standard for the diagnosis of HSV. Rare false-positive reports result from cross-contamination. False-negative reports have been described in neonates and young infants, perhaps because of the presence of heme or other inhibitors. In addition, false-negative assays can occur early in the disease.

Prompt therapy with acyclovir inhibits the herpes simplex polymerase and stops the virus from replicating. Patients with possible HSV are recommended to receive 10 mg/kg acyclovir intravenously every 8 hours. Rapid infusion can cause crystalluria and subsequent renal failure. The dose should be given slowly over at least 1 hour by pump infusion techniques. A therapy duration of 10 days is suggested, but this may result in up to a 10 percent relapse rate. A longer therapy period of 3 weeks has been proposed.

Japanese Encephalitis

Japanese encephalitis virus (JEV) is a flaviviral neurologic infection closely related to St. Louis encephalitis and West Nile virus. The disease is spread throughout rural areas of India by culicine mosquitoes, most often *Culex tritaeniorhynchus*. It is the most common form of viral encephalitis in India. Japanese encephalitis is transmitted to humans via the bite of infected mosquitoes. The virus initially propagates at the site of the bite and in regional lymph nodes. Subsequently, viremia develops, leading to inflammatory changes in the heart, lungs, liver and reticuloendothelial system. Most infections are cleared before the virus can invade the central nervous system (CNS), leading to subclinical disease. However, neurologic invasion can develop, possibly by growth of the virus across vascular endothelial cells, leading to involvement of large areas of the brain, including the thalamus, basal ganglia, brain stem, cerebellum, hippocampus, and cerebral cortex. Mortality rates in places with intensive care capabilities are 5-10 percent. In less developed areas, mortality rates may exceed 35 percent. Worldwide, more than 10,000 reported deaths occur per year. Approximately 33-50 percent of patients with symptomatic disease who survive have major neurologic sequelae at 1 year, including seizure disorders, motor or cranial nerve paresis, or movement disorders.

Most symptomatic infections in endemic areas occur in young children (aged 2-10 year) and elderly people. In infections in nonendemic areas, disease occurs in all age groups. Patients have a history of mosquito exposure in an endemic area. The incubation period ranges from 4-14 days, which is followed by a prodrome of fever, headache, nausea, vomiting, and myalgia, which may last for several days. Neurologic signs are varied. Generalized weakness, hypertonia, and hyperreflexia (including presence of pathologic reflexes) are common. Papilledema develops in less than 10 percent of patients, and 33 percent have cranial nerve findings (e.g. disconjugate gaze, cranial nerve palsies). Extrapyramidal signs frequently are observed, including masklike facies, tremor, rigidity, and choreoathetoid movements.

Lab studies include complete blood cell count (CBC) which often shows a nonspecific, modest leukocytosis in the first week of illness. A mild anemia also may be present. Serum sodium may be depressed because of inappropriate antidiuretic hormone secretion. MRI and a CT scan often show bilateral thalamic lesions with hemorrhage. The basal ganglia, putamen, pons, spinal cord, and cerebellum also may show abnormalities.

EEG often reveals diffuse continuous delta slowing or diffuse delta pattern with spikes. A correlation does not exist between EEG changes and the severity of Japanese encephalitis or its outcome.

CSF protein is mildly elevated in most cases. Between 10 and several hundred mononuclear white blood cells may be observed on cell count. Virus can be isolated from the blood during the first week of illness. The CSF rarely will yield virus, except in severe or fatal cases. IgM capture enzyme-linked immunoassay (ELISA) of serum or CSF is the standard diagnostic test for Japanese encephalitis. Sensitivity is nearly 100 percent when both serum and CSF are tested. False-negative results may occur if the samples are tested too early (e.g., within first week of illness). Some cross-reactivity may arise from other flaviviruses (e.g. dengue and West Nile virus) and from Japanese encephalitis and yellow fever vaccinations. New IgM dot enzyme immunoassays for CSF and serum are portable, simple tests that compare favorably to the capture ELISA for field diagnosis (sensitivity 98.3%, specificity 99.2% when compared to capture ELISA as standard).

Therapy for symptomatic Japanese encephalitis infection is supportive. Patients often require feeding, airway management, and seizure control. No clearly effective antiviral agents exist. Prognosis in symptomatic infections varies. Controlled studies have not been conducted. A significant number of patients who survive acute Japanese encephalitis develop residual neurologic deficits. Disabilities may range from subtle changes in behavior to serious problems, including blindness, ataxia, weakness, and movement disorders. Serious residual neurologic problems developed in as many as 50 percent of symptomatic patients at 1-year follow-up visits. Case-mortality rates may range from 20-50 percent.

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CHAPTER

Bacterial, Viral and Fungal Meningitis

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Inflammation of the central nervous system includes three specific pathological diagnoses that often are clinically indistinct upon presentation: meningitis, encephalitis and meningoencephalitis. All three pathologic states result from foreign agents stimulating inflammation in the central nervous system (CNS). Bacteria, viruses, fungi, drugs and non-pharmacologic chemicals can stimulate the inflammatory cascade within the central nervous system. Meningitis is an inflammation of the meninges in the spinal cord and dura, and causes cerebral spinal fluid (CSF) evidence of inflammation resulting in the classic stiff or painful neck. Encephalitis involves the inflam-mation of the cerebral cortex with signs of confusion, coma, headaches and photophobia. Meningoence-phalitis represents inflammation of both the meninges and the cortex resulting in a mixed clinical picture. Generally, critically ill patients with CNS inflammation present with a combination of signs pointing to an involvement of meninges and brain.

BACTERIAL MENINGITIS

Introduction

Meningitis presents commonly in a previously healthy patient that has rapidly developed symptoms and signs of infection with encephalopathy; the potential end result is often severe neurological sequelae or even death.

It is the intent of the authors that the readers of this chapter conceptualize meningitis as a complex brain injury with a predictable sequence of pathophysiological events. Although the inciting event in meningitis or encephalitis is an infectious agent, the central nervous system (CNS) injury, some of which is preventable or treatable, is largely due to the body's inflammatory response. A similar response to that seen in other forms of brain injury. Cerebral edema with an increase in intracranial pressure (ICP) and sudden brain herniation is often the fatal outcome of bacterial meningitis and occurs within 24 hours of medical attention. This time coincides with the increase in the inflammatory response generated by antibiotics and the therapeutic manipulation that the patient undergoes upon hospital admission. Recognizing the sequence of these events offers a window of opportunity to engage in strategies directed to attenuate brain damage as the infectious process is brought under control.

Etiology

While many infectious agents can cause meningitis the majority of patients suffer from meningitis of bacterial origin, that is the focus of this chapter. In the normal host, etiological agents are associated with the age of the patient. Table 87.1 depicts the most common pathogens grouped by age as well as the common susceptibility to antibiotics before culture and susceptibility are available.

Patients with ventricular shunts, basilar skull fracture, and/or postoperative from neurosurgical procedures have a high incidence of staphylococcal infection. Patients with immunosuppression (i.e., AIDS or post-chemotherapy) may be affected by

Table 87.1: Most common agents in bacterial meningitis

Age	More frequent bacteria	Infrequent bacteria
0 to 1 month	*Streptococcus agalactiae* (B group) Listeria monocytogenes Gram–(specially E. Coli and *Klebsiella* sp)	*Staphylococcus sp.* *Salmonella* *Pseudomonas aeruginosa* *Streptococcus pneumoniae* *Haemopillus influenzae*
1 to 3 months	*Streptococcus* B group Listeria monocytogenes Escherichia coli *Haemopillus influenzae B* *Streptococcus pneumoniae*	
3 months to 7 years	*Haemopillus influenzae B* *Streptococcus pneumoniae* *Neisseria meningitidis*	*Mycobacterium tuberculosis* *Staphylococcus* sp Streptococcus group B Listeria monocytogenes Gram-negative
> 7 years	*Streptococcus pneumoniae* *Neisseria meningitidis*	*Haemophillus influenzae* *Mycobacterium tuberculosis* *Staphylococcus* sp *Streptococcus* sp Gram-negative

Ref: Feigin RD, McCraken Jr GH, Klein JO. Diagnosis and management of meningitis. Pediatr Infect Dis J 1992;11(9):785-814.

unusual organisms. A complete treatment of which is beyond the scope of this chapter.

Clinical Presentation

Fever with altered consciousness (lethargy or irritability), headaches, nausea and vomiting or seizures are common presenting signs of meningitis. Stiffness of the neck and a bulging fontanel in the neonatal period may be present, but are often absent and cannot be used to rule-out the possibility of meningitis. If a patient present with coma, pupillary changes, cranial nerve dysfunction or an altered respiratory pattern, it should be assumed to have increased intracranial pressure. The absence of papilledema on fundoscopic exam does not rule out increased ICP. Focal neurological deficit is a poor sign and is often secondary to areas of infarct. A petechial or purpuric rash could be seen with *N. meningitidis*, shock could be the initial presenstation in *H. influenzae*. Neonatal meningitis presents with non-specific symptoms or physical findings, a high index of suspicion and a lumbar puncture (LP) are needed to reach a diagnosis. Bacterial pathogens are primarily associated with the maternal genitourinary tract.

Patients at Risk of Neurological Injury

Upon presentation a poor response to pain, a Glasgow Coma Score of < 8, the presence of focal neurological deficit, a forced gaze, or the presences of pupillary abnormality are symptoms associated with poor prognosis. The presence of hypotension, shock, a peripheral WBC < 5,000 mL^3, a serum Na < 135 mEq/L, or in the CSF a WBC < 1,000 mL^3, a protein > 250 mg/dl or a glucose < 20 mg/dl have also been associated with poor outcome.

In neonates, within 12 hours of admission, the presence of coma, prolonged seizures, need for inotropes, or leukopenia (WBC < 5,000 mL^3) are associated with poor prognosis.

Pathogenesis

Aggregate brain injury is a result of a primary cerebral insult coupled with the development of secondary cerebral injury. The primary insult occurs in areas of that suffer ischemia and necrosis secondary to vasculitis, or areas with cerebritis secondary to neutrophil infiltration. The secondary injury is a sequence of biochemical and physiological processes that exacerbate existing brain injury. The cerebral blood flow is altered with regional areas of ischemia while other areas are subject to hyperemia. Blood-brain barrier disruption contributes to the production of vasogenic edema. Damaged neurons liberate excitatory amino acids with detrimental stimulation to the surrounding cells. Secondary insults are often exacerbated by physiological instability leading to inadequate brain substrate for brain metabolism. Instability leading to tissue hypoxia (hypoxemia) and ischemia (hypotension) or increased unfulfilled metabolic demands (seizures and fever) results in a worsening of the secondary injury.

The offending agent may enter the CNS by hematogenous spread or by direct invasion. Bacterial colonization, most commonly in the nasopharyngeal area, often precedes invasion into the blood stream and bacteremia. The choroid plexus, rich in blood vessels, is a common point of entry into the CSF during bacteremia. When continuity of the dura mater (basilar skull fracture, post- neurosurgical procedure) has been disrupted or there are adjacent infectious process (i.e., sinusitis, orbital cellulitis) the point of entry is a direct route into the subarachnoid space. Outbreaks of meningitis sometimes occur 4-6 weeks after seasonal epidemics of influenzae or other respiratory viruses. It is postulated that these viral infections may weaken immune defenses allowing colonizing bacteria to become invasive. Clusters of meningococcal disease are seen in adolescents and young adults living under close conditions such as residential schools and in military recruits. In neonates, maternal fetal transmission occurs within the delivery period. Group B Streptococcus may be associated with other signs of sepsis or develop as an indolent encephalopathy in the neonate.

The CSF has limited mechanism to counteract infection and a rapid bacterial replication ensues. When bacteria replicates or dies, fragment of the bacteria are liberated acting as toxic agents triggering an inflammatory reaction. Following antibiotic therapy rapid bacterial lysis results in the massive release of bacterial cell wall and membrane fragments (i.e., lypopolysaccharides, techoic acids, etc). These bacterial products stimulate stationary macro-phages, astrocytes, glial cells and other brain cells. The stimulated cells liberate several pro-inflammatory mediators, cytokines (e.g., IL-1 and TNF α), chemokines, and matrix-metalloproteinases creating a positive feed back loop for the inflammatory cascade. Neutrophil margination followed by migration into the CSF occurs exacerbating the inflammation with deleterious effects to the brain parenchyma. Reactive oxygen (O_2 free radicals) and nitrogen species, that are highly cytotoxic, are liberated through multiple pathways. The blood-brain barrier is composed of vascular elements with tight junctions surrounded by glial cells, lose their tight junction resulting in open gates where capillary leak occurs with diffusion of low molecular weight proteins (i.e., albumin). Endothelial cell dysfunction ensues producing cerebral blood flow alteration, vessel wall irregularities with vasculitis and thrombosis. Intracranial pressure rises as a consequence of multiple mechanisms including a decreased outflow of CSF, regional areas of hyperemia, vasospasm, vasogenic and cytotoxic edema. Thrombosis of basilar vessels or the venous sinus could occur with devastating consequences.

Brain Injury

Aggregate brain injury is a result of a primary cerebral insult coupled with the development of secondary cerebral injury. The secondary injury is a sequence of biochemical and physiological processes that exacerbate existing brain damage as well as secondary insults. Primary insult occurs in areas of that suffer ischemia and necrosis secondary to vasculitis, or areas with cerebritis secondary to neutrophil infiltration. The cerebral blood flow is altered with regional areas of ischemia while other areas undergo hyperemia. The blood brain barrier disruption contributes to the production of vasogenic edema. Damaged neurons liberate excitatory amino acids such as glutamate with detrimental stimulation to the surrounding cells. Secondary insults are often the result of physiological instability leading to inadequate brain substrate for brain metabolism, like tissue hypoxia (hpoxemia) and ischemia (hypotension) or increased unfulfilled metabolic demands (seizures and fever).

Critical Period

Patients with meningitis often deteriorate after the initiation of the antibiotic therapy. Animal models and human studies show an exacerbation of inflammation and intracranial pressure within the initial 12 hour after antibiotic therapy is initiated. Acute deterioration with episodes of herniation has been described during the initial 24 hours of hospital admission. Episodes of brain herniation have been associated with procedures (i.e., spinal tap, intubation) or transport and mobilization of the patient (inter-transport facility, transport to radiology). Identifying patients at high risk of suffering neurological injury and recognizing crucial period in the medical management may allow tailoring therapies to alter the outcome.

Lumbar Puncture

The definitive diagnosis is obtained by examination and obtaining culture of the CSF. However, the lumbar puncture (LP) is contraindicated in patients who are unstable or have signs of increased intracranial pressure (patients with Glasgow Coma Score < 8, pupillary asymmetry or focal neurological deficits). Positioning the patient for the LP can exacerbate increased ICP precipitating cerebral herniation. Furthermore, the LP rarely changes the empiric initiation of antibiotic therapy. If there is a strong clinical suspicion of bacterial meningitis in a patient at risk of increased intracranial pressure it is recommended that the LP be delayed until the patient is clinically stable and outside the critical period. Up to two days of antibiotic therapy do not appreciably affect CSF findings that will demonstrate inflammation if the spinal tap is deferred, and therefore, steroids and antibiotic therapy should not be postponed. Inflammation will still be demonstrable if the spinal tap is deferred, though culture results are likely to be obfuscated.

The computed axial tomography (CT) scan can not be utilized to guarantee that is safe to perform an LP. The CT scan may show cerebral edema, but it lacks sensitivity to rule out the presence of increase ICP. However, CT scans can determine the presence of an epidural or subdural empyema or other indications for surgical intervention.

The hallmark of meningitis, though not so with encephalitis, is that the CSF will reveal abnormal findings (Table 87.2).

The presence of neutrophils with an increased protein and a serum to CSF glucose ratio less than 50 percent are the typical findings in CSF for bacterial meningitis. However, the CSF may have some but not all these disturbances. In particular the CSF at en early period may have a predominance of lymphocytes. Blood and urine cultures should be obtained. Tests for latex agglutination have widely different sensitivities and cross-reactivity, the most commonly utilized are performed in urine samples. They may have a place in the diagnostic work up when LP can not be performed or in cases of partially treated meningitis. Sequential measurements of acute phase reactants, like C reactive protein (CRP), could be utilized as an imperfect guide in cases where the LP could not be performed or is traumatic. For the immunocompromised patient specific stains (India ink), cultures for fungus and tuberculosis as well as special antigens (Cryptococcal antigen) should be performed.

Table 87.2: Characteristics of the CSF in bacterial meningitis and encephalitis

LCR	*Bacterial meningitis*	*Viral meningitis*
N white forms	↑ (mostly > 1000/mm^3) Neutrophils	↑ (10-2000/mm^3) Lymphocytes
Glucose	↓ (< 40 mg/dl)	Normal (> 45 mg/dl)
Relation glucose CSF/blood	< 0.3	> 0,6
Proteins	↑ (> 100 mg/dl)	Normal or discrete ↑
Bacterioscopic	Bacteria found in the non-treated patient	Bacteria not found
Cultural	Positive	Negative

Modified from: Philips EJ, Simor AE. Bacterial meningitis in children and adults. Postgr Med 1998;103:102–17.

Indications for Admission to the PICU

Cardiorespiratory instability, a rapid clinical deterioration, a GCS < 8, or any of the above mentioned factors for patients at risk to develop a neurological injury are indications for a PICU admission. In infants it is difficult to discriminate between a GCS of 8 and 10 (Table 87.3).

In many institutions in the United States patients with a high index of suspicion are admitted for observation during the critical period regardless of the initial presenting signs and symptoms. Changes in vital signs, examination or other laboratories indicating a generalized septic process should also warrant a PICU admission, e.g. thrombocytopenia, pethechiae, hyponatremia, neutropenia, severe acidosis. It is important to stress that aggressive surveillance is needed in the initial 24 hrs after the patient has sought medical attention for presumptive bacterial meningitis.

Treatment

Cardiorespiratory Management

Maintenance of high tissue oxygenation with normocapnia and a stable airway is the objective. The cerebral blood flow could be substantially decreased globally with significant regional variability. Hyperventilation with subsequent hypocapnia should be avoided because it can reduce cerebral blood flow triggering ischemia in regions of the brain. Studies in traumatic brain injury indicates that the administration of a high percent of inspired oxygen (FiO_2) during the period of decreased cerebral blood flow can improve brain tissue oxygenation. While no studies have been performed in meningitis this approach seems intuitively correct.

Table 87.3: Glasgow coma score modified for infants

Eye opening response	
Spontaneously	4
To verbal command (to shout)	3
To pain	2
No response	1
Best motor response to painful stimuli	
Localizes pain	5
Flexion-withdrawal	4
Abnormal flexion	2
Flaccid	1
Best verbal response	
Cries	6
Does not cry	1

It is possible that the laryngeal reflex may be lost when the patient has a GCS < 8. In this cases the airway should be protected with an elective intubation with the assumption the patient has an increased ICP. Intubation can trigger a significant increase in ICP and episodes of brain herniation, so that the most skillful individual should perform the procedure. Intubation should be performed with the induction of deep sedation (e.g. Thiopental 5 mg/kg and lidocaine 1.5 mg/kg) and paralysis to avoid triggering a sudden increase in ICP.

Blood pressure: Several studies have shown a dependency of cerebral blood flow on the mean arterial pressure with the conclusion that autoregulation could be impaired in several cases. Blood pressure should be maintained normal to high normal to preserve cerebral perfusion pressure. Hypotension and severe hypertension should be avoided and aggressively treated.

Dexamethasone

If there is a suspicion of meningitis we recommend use of dexamethasone in a dosage of 0.6 mg/kg per day in two to four divided doses for 2 to 4 days. The optimal initial dose of steroids should be infused before or with the initial dose of parenteral antibiotics. Dexamethasone is capable of inhibiting the production of cytokines only before the occurrence of the lysis of bacteria secondary to antibiotic therapy. Once cytokines are release steroids cannot modulate inflammation. Dexamethasone does not affect that adequate levels of antibiotic penetrate into CSF. Dexamethasone has no adverse effect on aseptic meningitis or herpes encephalitis.

Antibiotics

Table 87.4 illustrates the most common sensitivities of pathogens associated with an age of presentation or a particular condition. Immunocompromised patients often present with different organisms. Resistant strains of the *S. Pneumoniae* to penicillinas and third generation cephalosporins are emerging dictating, in some geographical areas, the concomitant initial administration of vancomycin. Once the susceptibility of the organism is available

Table 87.4: Empiric initial antibiotic therapy in bacterial meningitis

Age/condition	*Antibiotics*
Newborn	Ampicilin + cefotaxime or Ampicilin + aminoglicosides
1 to 3 months	Ampicilin + cefotaxime or cetriaxone
> 3 months	Cefotaxime or ceftriaxone
Neurosurgical procedure	Vancomycin
Shunt malfunction	

the initial broad-spectrum antibiotic therapy should be narrow to the specific sensitivity.

Fluid Therapy

Infection or injuries to the CNS result in increased secretion of antidiuretic hormone (ADH). However, several studies in meningitis indicate that ADH secretion is most likely secondary to hypovolemia. ADH is increased during the first few days of clinical symptoms and the reduction during the following days is proportional to the amount of sodium administered and is dependent on the restitution of normovolemia. Several studies also point that clinicians are unable to accurately assess the fluid status of patients with meningitis. Early fluid restriction has shown to worsen the outcome. The syndrome of inappropriate secretion of ADH (SIADH) necessitating fluid restriction is more rare that it was thought a few years ago. Fluid management should consist of a rapid administration of fluid as bolus of isotonic solutions (NS, RL, or 5 percent Albumin) when there are signs of hypoperfusion or blood pressure instability. Subsequent fluid should consist of isotonic solutions (NS) full maintenance (1.500 cc/m^2/day). Glucose is added if the patient is a neonate, or an infant who is hypoglycemic being careful to avoid hyperglycemia which can exacerbate brain damage. Electrolytes are added as appropriate. Hypotension, hyperglycemia, hypoglycemia and probably hypoalbuminemia should be avoided because they may contribute to subsequent neurologic injury.

Severe Meningitis

This approach applies the principles of improved cerebral perfusion and oxygen delivery in all patients with techniques to decrease oxygen consumption in the most severely affected. Current recommendations include lowering ICP, maintaining an adequate cerebral perfusion pressure and avoiding hyperventilation (Table 87.5).

Table 87.5: Guideline for patients with suspected ICP

- Obtain stability in particular in the initial 24 hrs
- Secure airway, maintain high oxygenation and normal carbon dioxide
- Maintain a stable intravascular volume and blood pressure
- Head midline elevated 30 degrees.
- Normal or high osmotic pressure
- Normal oncotic pressure
- Prevent/treat excessive metabolic demands, i.e. seizures, agitation, hyperthermia
- Monitor ICP if coma, CGS < 8, pupillary asymmetry or other signs of increased ICP
- Avoid maneuvers that can increase ICP, i.e. lidocaine before suction.
- If ICP is increased consider 3 percent saline, hypothermia, pentobarbital coma.

When to monitor ICP Patients with a GCS less than 8 have increased ICP, many of them have lost the autoregulation and they could experience episodes of low cerebral blood flow. Intracranial hypertension appears early in patients with coma reaching a maximum in the initial 24 hrs. Opening ICP and maximal ICP having nearly the same values. Therefore, patients at risk of neurological injury (see above) should be considered for placement of invasive ICP monitoring devises early in the critical period (initial 24 hrs) Survivors of severe meningitis exhibit a minimal cerebral perfusion pressure of 42 ± 9 mmHg. Obtaining a CPP above 45-50 mmHg seems to be an appropriate goal. The placement of invasive monitors has not been associated with dissemination of the infection or the development of abscesses.

Blood pressure stability and oxygenation are paramount to avoid sudden dilation of cerebral vessel secondary to hypotension or hypoxemia. Avoidance of intravascular dehydration will contribute to their stability. An arterial line and a line monitoring central venous pressure are necessary. Decrease all excessive metabolic demands like fever and seizures. Fever increases cerebral metabolism and could be detrimental to areas that suffer ischemia. If necessary in intubated patients' use cooling blankets to avoid hyperthermia. If shivering occurs paralyzing agents could be used for a brief period of time. Adequate sedation with an opiod or benzodiazepine will prevent changes in intrathoracic pressures that will affect the jugular venous drainage.

Having the head of the patient elevated at 30 degrees and in a midline position seems to be indicated to facilitate venous drainage. Aggressive treatment of seizures with a benzodiazepine followed by phenytoin (loading dose 20 mg/kg) or phenobarbital (loading dose 20 mg/kg) to prevent further episodes is indicated.

Increased ICP should be treated with methods other than hyperventilation with the exception of brief period of time. There are regional differences in cerebral blood flow creating zones of ischemia if patients are hyperventilated.

Novels Therapies

Hypertonic Saline: The utilization of 3 percent hypertonic saline as a bolus (5-10 cc/kg over 20 min) or as continuous infusion to increase serum sodium and decrease cerebral edema while preserving intravascular volume is being favored rather than mannitol. While no studies address this issue in meningitis hypertonic saline is rapidly gaining popularity for the treatment of intractable ICP. It may have a role in the initial management, but studies are lacking on this regard.

Hypothermia: Moderate hypothermia (32-34°C) plays a role in protecting neurons by modifying multiple points of the cascade of events that leads to secondary brain injury. In animal models, hypothermia attenuates blood-brain barrier dysfunction, reduces the release of excitatory amino acids, modulates the inflammatory reaction, and decreases cerebral edema and intracranial pressure. Spontaneous hypothermia may be a normal mechanism of the brain to protect during period of injury. Cerebral metabolic rate decreases approximately 7 percent for each degree celsius reduction in temperature. In traumatic, hypoxic and ischemic brain injury, external warming of patients (above 32°C) that spontaneously exhibit hypothermia is detrimental. Induced hypothermia is effective in treating refractory intracranial pressure. While inducing hypothermia cannot be recommended as first line of therapy it should be considered for cases with refractory intracranial pressure.

Complications

Approximately 20-30 percent of patients have seizures before or during their hospitalization. Persistent seizures could be a problem indicating that parenchymal areas have being affected. All children require hearing evaluation at the end of therapy or on follows-up exams. Up to 30 per-cent of patients with pneumococcal meningitis suffer sensorineural hearing loss. Subdural effusions occur in approximately 15-30 percent of infants. They can be associated with fever and occasionally with increased ICP secondary to mass effect, but generally are inconsequential and do not need to be evacuated. By contrast, subdural empyema can produce fever, irritability or meningeal signs, and needs surgical evacuation. The CT scan with contrast can distinguish between these two entities. Persistent fevers without a clear origin is a common occurrence. After other causes have been ruled out central line infections need to be suspected; drug originated fever are unusual. Septic and aseptic sinus thrombosis may occur during the disease process, often with unfavorable outcome, in particular if they are associated with venous infarcts. Thrombosis of the cortical veins is usually associated with occlusion of a major dural sinus. In this case the risk of developing intracerebral hemorrhage is high and anticoagulation is not recommended. Antibiotics or the use of anticoagulation may be indicated in relation to the type and location of the thrombus. Arterial complications with stenosis of major and medium-sized arteries, vessel walls irregularities, focal dilatations and occlusion of distal branches, may occur. There is no established therapy for these entities, taking on account that arterial complications are secondary to intense meningeal inflammation it seems reasonable to use dexamethasone.

Control Measures

The general guidelines are the following, however, updates may be occurring after the publication of this text.

Streptococcus pneumoniae: Prophylactic antibiotic treatment of contact for is not recommended.

Neisseria meningitidis: Chemoprophylaxis is recommended for close contact with patients, with exposed household, school or childcare contacts must be observed carefully and rapidly brought to medical attention if a febrile illness develops.

Close contacts are household members, child care or nursery school contact during previous 7 days, exposure to secretions (i.e. kissing or sharing eating utensils or toothbrush), mouth to mouth resuscitation, unprotected contact for mechanical intubation.

Haemophilus influenzae: Chemoprophylaxis is recommended to all household contacts if (1) there is a child younger than 1 year of age that has not complete the immunization schedule against *Haemophilus influenza,* (2) if there is a child younger than 12 month of age, (3) if there is a child with an immunocompromised status. Nursery and child care centers contacts when 2 or more cases have occurred within 60 days.

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FUNGAL MENINGITIS

INTRODUCTION AND INCIDENCE

Candida

Candidal species cause a broad range of infections from being mucocutaneous involvement to life-threatening invasive disease including meningitis. *Candida* is ubiquitous in the environment with more than 150 species, but only about 10 species are responsible for the majority of disease.[1,2] *C. albicans* is the most common etiologic agent, though invasive disease is increasingly caused by non-albicans species. Other species causing disease in man include: *C. tropicalis, C. parapsilosis, C. glabrata, C. krusei, C. guilliermondii, C. lusitaniae, C. lipolytica* and *C. stellatoidea.* In an article exploring candidal meningitis (CM) in children undergoing chemotherapy 11 of 12 infections were with *C. tropicalis* and only one with *C. albicans.*[3] In two Brazilian studies, candidal infections with non-albicans species were greater than or equal to half of the infections.[4,5]

The mortality associated with a disseminated candidal infection, including meningitis, is high and is due to a combination of factors including those factors that have predisposed the patient to developing the infection. In the two Brazilian studies previously cited, patients developing candidemia had a 40-50 percent mortality rate and in the study of CM in children with cancer all 12 patients died. 3-5 Persons at risk for developing CM include: the very low birth weight newborn, patients with immune compromise (such as: steroid therapy, HIV, chemotherapy, neutropenia), those receiving hyperalimentation and intralipids, persons with diabetes mellitus, and those receiving treatment with broad spectrum antibiotics or having in-dwelling catheters.[2,6] Little is known about how Candida invade the CNS. An article looking at an in vitro model suggests that Candida can invade without disruption of the brain vascular endothelium.[7]

Diagnosis

Clinical Presentation

CM is just one of the possible CNS presentations of a central nervous system candidal infection. Others include cerebral microabscesses, or vascular lesions. The onset of CM is often subacute with the development of fever, headache and a decreased level of consciousness. Additional signs of meningeal involvement may also be present.[1,6] Support for making the diagnosis of CM should include careful evaluation for mucocutaneous candidal lesions and an ophthalmologic examination for retinal lesions.

Laboratory Diagnosis

Yeast and pseudohyphae can be identified by Gram stain or potassium hydroxide suspension of infected material. A positive blood culture should be considered as an indication of disseminated candidiasis. The CSF in patients with CM demonstrates a pleocytosis, high protein and a decreased glucose. Culture of the CSF is positive in about 80 percent of cases and microscopic evaluation is positive in about 40 percent of cases.[6] In a study in 12 pediatric oncology patients with CM a CSF pleocytosis was seen in only 25 percent of patients with abnormal chemistries seen in less than half. Culture was positive in all cases and Gram stain positive in 7 of 12 patients.[3]

Radiologic Findings

The CT scan of patients with CM may be normal or may demonstrate the non-specific finding of hydrocephalus with the improved resolution of MR imaging the vasculitic component of CM may be evident. Microabscesses are below the detection limit on CT but may be visible on MR. Macroabscesses will appear as space occupying lesions.

Treatment

Candidal meningitis has a high mortality rate and requires aggressive treatment. Patients developing candidal meningitis are often immunocompromised increasing their risk of having a non-albicans infection and a poorer outcome. The treatment of candidal meningitis should consist of amphotericin B with the addition of oral flucytosine. Amphotericin B does not readily cross the blood-brain barrier, but remains the primary agent. Flucytosine readily crosses the blood-brain barrier and is synergistic with amphotericin B.[2,8] In an experimental animal study comparing the efficacy and distribution of various lipid formulations of amphotericin with amphotericin B deoxycholate suggests that only 1 of 3 lipid preparations was equal or potentially superior to amphotericin B deoxycholate.[9]

Fluconazole is a well-tolerated anti-fungal agent with good IV and oral bioavailability. Fluconazole has good efficacy against *C. albicans,* but less so against non-albicans species. Because of the risk in immune suppressed individuals of having an infection from a non-albicans species fluconazole cannot be recommended as a first line agent in CM[3] additionally, there are reported treatment failures with fluconazole in the treatment of CM in children and delayed sterilization when compared to amphotericin B in animal models.[6,10,11]

Aspergillosis, Cryptococcus, Coccidioidomycosis, Histoplasmosis

Additional fungi known to cause invasive disease, including meningitis, include species of: *Aspergillus, Cryptococcus, Coccidioides,* and Histoplasma. All of these agents are ubiquitous in the environment and the mode of transmission is via the inhalation of spores. Infection does not occur via person-to-person contact. These fungal infections when presenting as systemic disease, including meningitis, have as a rule have the property of being opportunistic infections that are more common in immunocompromised individuals. This group will include: neonates, chemotherapy patients, patients on chronic steroids, transplant patients, patients with neutrophil dysfunction (such as persons with chronic granulomatous disease) and persons infected with HIV. In patients with HIV cryptococcosis is an AIDS defining illness. The symptom complex in meningitis from these agents include fever, behavioral changes and symptoms of meningitis, encephalitis or of a space occupying lesion. The onset of symptoms is often more indolent than in patients with acute bacterial meningitis.

Definitive diagnosis of these fungi can be made by culture of the organisms on an appropriate mycologic medium such as sabouraud glucose medium. The diagnosis of cryptococcal meningitis can be made by India ink preparation of the CSF. Non-culture tests for *Aspergillus* include detection of the galactomannan antigen by ELISA, antibody detection, and PCR. Detection with ELISA for the galactomannan antigen was the most sensitive of the non-culture methods in one study.[12] *H. capsulatum* detection can be performed by demonstration of intracellular yeast on biopsy material stained by Gomori's methenamine silver or by detection of polysaccharide antigen.

Amphotericin B is the treatment of choice for all of the listed infectious agents. The treatment of invasive *Aspergillus* disease is with amphotericin B in high doses (1.0 to 1.5 mg/kg/day) for 4 to 12 weeks. Additional therapies may include the concurrent treatment with rifampin or itraconazole or surgical debridement.[1,2,12] Amphotericin B in combination with oral flucytosine is recommended for cryptococcal meningitis. Combination therapy should continue for a minimum of two weeks or until CSF cultures are negative and then monotherapy with amphotericin B or fluconazole should continue for an additional four to ten weeks. Additional agents such as fluconazole or itraconazole may be indicated for individual clinical situations.[2,13] In all cases more pro-longed therapy may be necessary in immuno-compromised patients.[2,14] As in previous sections, specific recommendations for the treatment of meningitis due to these opportunistic fungal infections in patients with HIV/AIDS is beyond the scope of this chapter.

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HERPES SIMPLEX ENCEPHALITIS

Introduction and Incidence

The presumptive diagnosis of herpes simplex encephalitis is based on the presence of altered mental status, fever, cerebrospinal fluid findings and focality on physical or neurodiagnostic evaluation. Prompt treatment should be initiated upon suspicion. The neurological outcome is dependent on length of time from the presentation of clinical symptoms to the initiation of Acyclovir.

Herpes simplex 1 (HSV-1) and herpes simplex 2 (HSV-2) are involved in central nervous system (CNS) disease, but with differing age presentations, progression and prognosis. HSV-1, or oral herpes, is primarily responsible for HSV encephalitis outside the newborn period. HSV-2 is predominantly a sexually transmitted disease and is responsible for genital herpes infections and severe neonatal infections. There is overlap in the two diseases and the designation of oral and genital herpes infections should not be used to identify HSV-1 and HSV-2 infec-tions respectively. Additional members of the herpes-virus family include the varicella-zoster virus, human-herpes virus 6 and 7, CMV and Epstein-Barr virus. These viruses may produce nonacute encephalitis except in immunocompromised patients.

Herpes simplex infections, including cutaneous, mucosal, CNS and disseminated disease, in the newborn are primarily caused by infection with HSV-2. Transmission is accomplished by contact with infectious material in the vaginal canal or by ascending infection. The risk of contracting HSV at delivery can be as high as 50 percent in infants born vaginally to women with a primary infection. The isolation of HSV-2 in a pediatric patient outside the neonatal range should raise suspicion that the disease was venerally transmitted and concerns for child abuse should be entertained.

Herpes virus CNS infections outside the neonatal period are mostly due to HSV-1 infection. The majority of primary HSV-1 infections are asymptomatic and the most common presentation of an HSV-1 infection is gingivostomatitis.[1] An HSV-1 infections can have a range of presentations with encephalitis being among the most serious manifestations. An HSV-1 encephalitis has a biphasic age distribution, affecting patients 5 to 30 years or above 50.[2]

Diagnosis

Clinical Presentation

Three presentations predominate in neonates with herpes simplex viral infections including—CNS disease, disseminated herpes infection and infection of the skin, mouth and eyes. The most common and consistent aspects of the clinical presentation of patients with neonatal HSV encephalitis or meningitis are fever, irritability and seizures. In patients with CNS disease skin lesions may appear late or not at all and thus cannot be used as a way to exclude a diagnosis of herpes.[1] An HSV-2 CNS infection commonly presents as aseptic meningitis and tends to have a benign course.

In contrast to HSV-2 meningitis, HSV-1 encephalitis is characterized by fever, focal neurologic changes, an altered level of consciousness and/or seizures.[2] HSV-1 encephalitis may represent either a primary infection or a reactivation of an earlier infection. The most important outcome variable in the treatment of HSV encephalitis is the time to which antiviral therapy has begun, and this is often dictated by the clinical presentation of the patient. If the patient has progressed in their clinical presentation to a state of coma before the initiation of the antiviral therapy then the likelihood of intact recovery or survival is substantially diminished.

Laboratory Diagnosis

Lumbar puncture findings in HSV encephalitis usually demonstrate a normal glucose, and normal or elevated protein, WBC counts are elevated often in the range of 50 to 2000 cells/mm^3, with a predominance of lymphocytes. In approximately 75 percent of patients with HSV encephalitis the CSF contains red blood cells and this reflects the lytic and inflammatory processes inherent with this infection. Three to 5 percent of patients with severe encephalitis have normal CSF findings.[3] Viral culture for HSV shows a poor sensitivity and is isolated in less than 5 percent of patients with HSV-1 encephalitis.[4]

The current standard of diagnosing HSV CNS disease is by use of the polymerase chain reaction (PCR) to assess the presence of specific viral DNA in the CSF or serum. PCR has good sensitivity (95%) and excellent specificity (100%).[5] Additionally, as the availability of the technique and the materials become more common place turn around time is significantly reduced. In a study that examined follow-up patients with HSV encephalitis demonstrated continued PCR positive results for greater than 10 days after starting antiviral therapy.[6] There are case reports of initial negative PCR results that have proven to be positive later in the course of disease suggesting that if clinical suspicion is high continuing antiviral therapy and repeating the test may have value despite an initial negative result.[7] Prior to the advent of PCR techniques brain biopsy was considered the diagnostic method of choice for early and specific diagnosis, but despite having good specificity (100%) the sensitivity is only 60-70 percent.[2]

Serologic tests are not helpful in acute infection.[1,2] In general, herpes grows well in culture, with the exception of isolation from the CSF, with positive results available in 1 to 3 days after inoculation. Cultures should be obtained from sources including blood, skin, vesicles, mouth, nasopharynx and CSF. CSF cultures in patients with encephalitis of are usually negative.[1]

Radiological Findings

CT and MRI-Imaging of patients with herpes encephalitis demonstrates by CT analysis hypoattenuation of the anterior and medial temporal lobes and the inferior aspect of the frontal lobes. CT changes, however, are not usually apparent prior to the fifth day and the findings are often bilateral thought asymmetric. MRI is a more sensitive technique demonstrating low signal intensity in the temporal and inferior frontal lobes on T1-weighted images and increased intensity of T2 weighted images. In long-standing cases MRI may demonstrate atrophy and necrosis.[8]

Electroencephalogram (EEG): It may reveal a periodic high-voltage spike wave activity emanating from a temporal region and slow wave complexes at 2-3 seconds intervals.

Treatment

In all patients with suspected viral meningoencephalitis, supportive treatment is the mainstay of therapy. Supportive therapy in moderate to severe cases should include hospitalization, nutritional support, treatment of seizures and maintenance of adequate intravascular volume and blood pressure to support cerebral perfusion (See the treatment section on the treatment of bacterial meningitis for a detailed discussion of supportive care). Seizures are often difficult to treat during the acute period and require aggressive use of anticonvulsants. Sometimes status epilepticus is present without a motor component and is only manifested by altered level of consciousness.

HSV 1-2 infections are the only viral CNS infection for which viral therapy has been proved useful in a non-immunocompromised patient. Directed treatment of suspected HSV-1 and HSV-2 infections should be initiated at presentation and should not await confirmation of a herpes infection. The most significant factor in determining outcome and avoiding the morbidity and mortality is the length of time until the initiation of treatment. We initiate Acyclovir empirically when the patient shows acute encephalopathy, fever, new onset of seizures or focality and HSV can not be ruled out. Acyclovir given intravenously for 21 days is the standard of care for HSV meningoencephalitis. The dose of Acyclovir in neonates is 60 mg/kg/day and 30 mg/kg/day beyond neonatal the neonatal period.[1,4] In Acyclovir resistant or refractory cases a change to foscarnet has been suggested.[5] Additionally, future therapeutic options include the addition of interferon a or b, and monoclonal antibody or hyperimmune serum against HSV infections.[9-11]

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TUBERCULAR MENINGITIS

Introduction and Incidence

The most common presentation of a *M. tuberculosis* infection is pulmonary with occasional extrapulmonary infections like disease of the skin, bones, joints, middle ear and mastoid and the central nervous system.[1,2] Risk factors for developing TB include: immunodeficiency (including HIV), prolonged high-dose corticosteroids, chemotherapy, overcrowding and malnutrition.[2]

Tuberculosis meningitis (TBM) represents 3 to 10 percent of the cases of TB.[3,4] The mortality rate of TBM varies between 15 and 25 percent with a study of PICU patients having a 75 percent mortality.[5-7]

Diagnosis

Clinical Presentation

Central nervous system infection with tuberculosis has 5 primary presentations. These are presentations that can appear independently or as a mixed disease. They include: pyogenic meningitis (TBM), serous tuberculous meningitis, a tuberculoma, a tuberculous brain abscess or spinal tuberculous leptomeningitis. The first stage of TBM is characterized by irritability, anorexia, listlessness and some fever. The onset is often gradual and symptoms develop over a couple of weeks. As the disease progresses into the second stage signs of increased intracranial pressure, stiff neck, cranial nerve palsies and seizures occur. Irregular vital signs, coma and rising fever characterize the third stage.[1]

TBM has a predilection for involving the base of the brain resulting in cranial nerve involvement as well as the development of hydrocephalus. Advanced stages of TBM are most often (approximately 80%) accompanied by hydrocephalus. About one-third of these patients have a non-communicating hydrocephalus.[6] In a Turkish study the majority of children presented with advanced (stage II or III) disease and had evidence of pulmonary involvement.[5]

Laboratory Diagnosis

Tuberculin skin testing (TST) is a useful tool for diagnosing TB infection and previous immunization with BCG is not a contraindication to skin testing. TST positivity occurs 2 to 12 weeks after the initial infection and may be useful if a TB infection is suspected. A negative TST does not exclude TB. Immune suppression, young age, poor nutrition, concurrent viral infection and a severe disseminated TB infection can cause a false negative result.[1]

M. tuberculosis can be obtained for culture from multiple sources including CSF. M. tuberculosis culture is not very sensitive and because of its slow growth cultures can take from 2 to 6 weeks even under optimal growing conditions with radiometric detection. Imaging of AFB in clinical samples including sputum, gastric aspirates, pathologic samples and CSF should be performed. The yield in these studies is improved if fluorescence microscopy rather light microscopy is performed on submitted samples. However, in a study of 213 patients with TBM only 13 percent had evidence of AFB on CSF smear.[5]

Radiologic Findings

Radiologic evaluation for suspected TB meningitis should include a CXR secondary to the high incidence of concurrent pulmonary involvement and a head CT because of the equally high incidence of obstructive hydrocephalus seen in TBM.[6,7] Poor correlation was found between ventricular size and ICP, though in children with communicating hydrocephalus a small or absent subarachnoid space correlated was correlated with higher CSF pressures.[6]

Treatment

The 2000 Red Book recommendations for the treatment of TBM include 2 months of isoniazid (INH), rifampin, pyrazinamide and streptomycin, followed by 7-10 months of INH and rifampin Capreomycin or kanamycin can be given in areas where streptomycin resistance is high or the isolate is shown to be resistant to streptomycin.[2] Adverse reactions to antitubercular drugs include hepatotoxicity to INH, rifampin and pyrazinamide, myalgias and thrombocytopenia to rifampin and nephrotoxicity with streptomycin. This is a partial listing of the serious adverse reactions to these medications and because of the prolonged nature of the treatment completing a full course of treatment can be difficult. In areas where barriers to health care are more pronounced adequate treatment is made even more problematic.

Corticosteroids are recommended as adjunctive agents in the treatment of TBM, though their use is not without controversy.[2] Current recommendations are for prednisone, or its equivalent, at a dose of 1 to 2 mg/kg/day for 6 to 8 weeks. In a prospective randomized controlled study of steroids versus no steroids in TBM steroids did not affect ICP or the development of hydrocephalus, but did improve mortality in patients with stage III TBM and improved IQ in survivors.[8] Additional medications that may have efficacy in the treatment of TBM include the drug thalidomide. Thalidomide is thought to be affective by virtue of its anti-inflammatory properties.[9]

An added note of caution in treating patients with TBM. The worldwide increase in TB, and particularly the appearance of multi-drug resistant TB, make it important that knowledge of local resistance patterns are employed when starting empiric therapy. Because of the slow growth of TB sensitivity data may not be available in a timely fashion. Co-infection of TB with HIV is significant problem, but the treatment of patients with TBM and HIV infection is outside the scope of this chapter.

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CHAPTER

88

Sedation, Analgesia and Neuromuscular Blockade

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One of the fundamental tenets of providing care to the critically ill children is to relieve suffering and reduce anxiety. Critically ill children who are conscious experience fear, normally far in excess of what bedside caregivers can appreciate. Agitation is the motor restlessness that accompanies anxiety. Pain is a common accompaniment critically ill children experience due to wounds, incisions or indwelling catheters and pain further amplifies the fear. Finally, the children confined to the pediatric intensive care unit (PICU) bed are sleep deprived,[1] which occurs from frequent interruption of patient routine and continuous stimulation with light, touch and noise originating from alarm systems of ventilators, pulse oximeters, intravenous (IV) infusion pumps and continuous electrocardiographic and hemodynamic monitoring. All of the above problems can be taken care of by maximizing the quality and length of sleep with minimal or no pain and anxiety.

In this chapter, we describe the practice of sedation and analgesia at MAX Hospital, Delhi in pediatric patients in the intensive care setting.

Definitions

Moderate Sedation/Analgesia (Conscious sedation)

A drug induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. Reflex withdrawal from a painful stimulus is not considered a purposeful response. No interventions are needed to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained.

Deep Sedation/Analgesia

A drug induced depression of consciousness during which patients cannot be easily aroused, but respond purposefully after repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patient may need help in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained.

Anesthesia

Drug induced loss of consciousness during which patient can not be aroused, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patient needs help in maintaining airway and positive pressure ventilation may be needed because of depressed spontaneous ventilation or drug induced depression of neuromuscular function. Cardiovascular function may be impaired.

Main Goals of Sedation

Sedation is given to achieve following goals:

i. To attenuate fear and anxiety.
ii. To potentiate analgesia
iii. To reduce unnecessary recall (amnesia).

In addition, sedatives are used to reduce metabolic demands particularly during circulatory shock; to facilitate tolerance to procedures and as a mandatory adjunct to neuromuscular blockade.

Indications of Sedation

Common indications of sedation in the PICU include mechanical ventilation and various procedures performed in the PICU. In addition, other areas of the hospital that commonly require sedation of pediatric patients include *endoscopy* and *radiology.*

It should be emphasized that the most important indication of sedation is any situation requiring anxiolysis and analgesia to comfort the child. Also, sedation potentiates the effect of narcotics, thereby ensuring better comfort and analgesia.

Sedation is a mandatory prerequisite prior to, and during administration of neuromuscular blockers.[2] The patient should never be subjected to paralysis without sedation. An additional benefit of sedatives like propofol and benzodiazepines is that of amnesia, and opiates provide analgesia in addition to sedation.

Procedures Requiring Sedation

Most common procedure requiring sedation in PICU is endotracheal intubation and mechanical ventilation. In addition to mechanical ventilation many other procedures require sedation (Table 88.1).

Many of these procedures can only be done in Radiology department, such as CT (computerized tomographic scan), MRI (magnetic resonance imaging) or radiation therapy, therefore, oxygen, suction and resuscitative and monitoring equipment should be available and only trained and experienced personnel should be administering sedation to ensure safety of the pediatric patient. As much as possible, PICU procedures should be planned ahead of time, so adequate preparation can be made in PICU (for example, flexible fiberoptic bronchoscopy; renal, liver or bone biopsy and high risk endoscopy).

Table 88.1: Procedures requiring sedation

1. *Non-invasive procedures*
   a. Magnetic resonance imaging (MRI)
   b. Computerised tomographic scan (CT Scan)
   c. Other imaging studies
   d. Radiation therapy
   e. Electroencephalography (EEG)
2. *Invasive and painful procedures*
   a. Bone marrow aspiration and biopsy
   b. Lumbar puncture or intrathecal medication administration
   c. Liver biopsy, renal biopsy or bone biopsy
   d. Dressing changes and wound or burn debridement
   e. Endoscopy, bronchoscopy
   f. Transesophageal echocardiography
   g. Thoracentesics or chest tube placement
   h. Paracentesis, pericardiocentesis
   i. Placement or removal of central line
   j. Fracture reduction or cast replacement
   k. Ultrasound guided aspiration of fluid collection in chest or abdomen.

Preprocedure Fasting and Risk of Aspiration

In order to decrease the possibility of aspiration if airway reflexes are lost, proper nil by mouth (NBM) status must be assured before an elective sedation. Standard accepted *American Society of anesthesiologists (ASA) Recommendations* given below, can be tailored to the individual patient age group as applicable:[3]

a. *Preterm* or *Newborn*—no milk 2 hours prior to sedation
b. *1-5 months*—no milk or solids 4 hours prior to sedation
c. *6-36 months*—no milk or solids 6 hours prior to sedation
d. > *36 months*—no milk or solids 8 hours prior to sedation

Six to eight ounces of clear liquid may be ingested upto two hours before the procedure by patients with normal gastric emptying. Clear liquids include apple juice, pediatric electrolyte containing fluids, water or aerated drinks. Many include breast milk in the category of clear liquids. No pulp containing juices are considered clear liquids.

Routes of Sedation

There are two broad categories of routes commonly used for sedating a child.

i. Oral/Rectal route
ii. Intravenous (IV)/Intramuscular (IM) route.

Oral/Rectal route is best used for premedication before IV sedation as well as for short painless procedures such as CT scan. For longer noisy procedures such as MRI with contrast, IV sedation is invariably required.

IV sedation is delivered by two methods:

a. as a continuous IV infusion, or
b. as intermittent bolus injection.

Continuous IV infusion has the advantage of providing a more stable level of sedation which is more comfortable for the patient and more convenient for the nursing staff. However, over sedation can easily occur if larger amount of drug are cumulatively given. It may also increase the need for prolonged mechanical ventilation.[4] Bolus injection is usually given in response to patient arousal therefore less drug may be given over time. However it potentially exposes the patient to uncomfortable subtherapeutic troughs of the drug as well as toxic peak levels.[4]

CLINICAL PHARMACOLOGY OF COMMONLY USED SEDATIVES AND ANALGESICS

Benzodiazepines

The primary pharmacological action of benzodiazepines is sedation. They also provide for anxiolysis,[5,6] muscle relaxation, and anticonvulsant activity and induce anterograde amnesia. Benzodiazepines have no analgesic effects. Commonly used benzodiazepines are Diazepam and Midazolam. Lorazepam has recently become available in India. Diazepam and Midazolam have greater lipophilicity, enabling them to cross the blood brain barrier quickly. They have a much more rapid onset of action and are the appropriate choices among benzodiazepines when immediate sedating effect is required. Their long-term use causes dependency and abrupt discontinuation causes a withdrawal syndrome resulting in rebound agitation, and even seizures in some patients.

Midazolam

The most commonly used benzodiazepine is midazolam at our institution. IV diazepam however, remains the most commonly available and used sedative with equally good safety record and efficacy in most institutions, due to lower cost compared to Midazolam. Dose of midazolam is age dependent. Because midazolam is water soluble, peak effects are not reached immediately, it is essential to wait 2-3 minutes to fully evaluate the sedative effect before starting the procedure or administering a repeat dose.

The dose needs to be titrated:

a. In patients 6 months–5 years of age an initial IV dose of 50-100 mic/kg is recommended, a total dose of upto 600 mic/kg may be required, but usually does not exceed a total of 6 mg.
b. In patients 6-12 years of age an initial IV dose of 25-50 mic/kg is recommended, a total dose of 400 mic/kg may be required, total dose not exceeding 10 mg.
c. Patients aged 12–16 years should be treated as adults.

Sedation for short procedures: Midazolam and other benzodiazepines are useful as sole agents for procedures that do not require analgesia. For sedation prior to short diagnostic or endoscopic procedures, midazolam may be used alone or in combination with ketamine or opiate agonist.[7] For peroral procedures, e.g., (upper gastrointestinal endoscopy, bronchoscopy), use of a topical anesthetic is recommended and for bronchoscopy, use of an opiate analgesic for premedication is also recommended. When used concomitantly with opiates, midazolam dosage should be decreased by 30 percent to adjust for sedative effect of opiates as well as to reduce chances of respiratory depression. The dose for short procedures is as described earlier. For maintenance of sedation midazolam may be administered in incremental IV doses of approximately 25 percent of the initial dose when lightening of sedation is evident.

Sedation in critical care settings. Midazolam is administered as continuous IV infusion. For sedation of intubated and mechanically ventilated patients Midazolam is initiated with an *IV loading dose of 50–100 mic/kg administered over at least 2-3 minutes.* The drug should not be administered as a rapid IV injection. The loading dose should be followed by continuous IV infusion to maintain the clinical effect. *Continuous IV infusion of Midazolam should be initiated at the rate of 1-2 mic/kg per minute; i.e. 60-120 mic/kg/hour.* The infusion rate may be increased or decreased generally by 25 percent of the initial or subsequent infusion rate to achieve the desired effect. *Nasal midazolam can also be used (0.05 to 0.34 mg/kg), same as rectal dose for minor sedation.*

Over dosage of midazolam produces symptoms that are extensions of the usual pharmacological effects of benzodiazepines such as sedation, somnolence, confusion, impaired coordination, diminished reflexes and hypotension. *Flumazenil,* a benzodiazepine antagonist can be used to reverse midazolam-induced sedation, if available in doses of 0.01 mg/kg IV titrated to effect up to 1-3 mg.

Diazepam

Diazepam is the prototypical benzodiazepine. Like midazolam it has a rapid onset of action and is the benzodiazepine of choice when immediate sedating action is required at bedside. Following an IV injection of 0.1 to 1 mg/kg, this drug is rapidly distributed to brain. The concentration in plasma declines rapidly owing to redistribution with an initial half-life of 10 to 15 minutes. However, drowsiness often returns with an increased concentration of diazepam in plasma after 6-8 hours. This effect is due to absorption from the gastrointestinal tract after excretion in the bile. Usage and adverse reactions are similar to midazolam. *Rectal diazepam (0.4-0.5 mg/kg)* can be used in emergency situations for seizure control (see chapter on Status Epilepticus).

Lorazepam

Lorazepam has an intermediate duration of action. It has no active metabolite, so it is a more steady agent for long term maintenance of sedation. Half-life of redistribution of this drug is more than twice that of diazepam, therefore onset of drowsiness is less rapid. It is useful when antero-grade amnesia is particularly desirable. Like midazolam it requires approximately one-third to half of the dose necessary for diazepam *(0.05 to 0.15 mg/kg with maximum of 2 mg).*

Opiates

Commonly used opiates are *morphine, fentanyl* and *pethidine (also known as meperidine).* The primary pharmacological action of opiates is to relieve pain or the sensibility to noxious stimuli via opioid receptors. Opiates provide no appreciable amnesia. A very significant secondary action of opiates is sedation and anxiolysis. Other effects include, emesis, urinary retention, ileus, respiratory depression and hypotension. Hypotension occurs due to a combination of venodilatation, sympatholysis, vagal mediated bradycardia and histamine release.

Morphine

Morphine has a half-life of 2-3 hours after IV administration. The active metabolite morphine-6-glucuronide accumulates in renal failure further extending the duration of action. Morphine should be given in smallest effective dose and as infrequently as possible to minimize the development of tolerance and physical dependence. The subcutaneous or IM dose of morphine sulphate in children is 0.1–0.2 mg/kg every 4 hours or as necessary. *Single pediatric dose should not exceed 10 mg IV dose in children is 0.05–0.1 mg/kg.* In children with severe chronic pain associated with cancer, morphine sulphate is given IV in dose of 0.025–2.6 mg/kg/hr. For post- operative analgesia, *maintenance IV infusion dose is 0.01–0.04 mg/kg/hr. with close monitoring for respiratory depression.*

Fentanyl

Fentanyl is a synthetic opiate with 100 times the potency of morphine. It has a more rapid onset of action due to greater lipophilicity. Duration of action is approximately 30 to 90 minutes due to shorter half-life. Fentanyl induces less hemodynamic instability because it does not induce histamine release like morphine. Therefore, fentanyl is the preferred choice in patients with circulatory shock. Like morphine it should be given in the smallest effective dose and as infrequently as possible to minimize the development of tolerance and physical dependence. As a word of caution, in neonates and younger infants, fentanyl can induce *chest wall rigidity* following rapid IV injection leading to severe respiratory depression, compounding the effect of centrally induced depression of the respiratory center. Use of muscle relaxants and immediate endotracheal intubation and ventilation is the treatment of choice for muscle rigidity induced by fentanyl.

As an adjunct to general anesthesia, *fentanyl may be given in low dose, moderate dose* or *high dose regimens*:

In the low dose regimens which is used for minor but painful surgical procedures an IV dose of *2 mic/kg* is administered.

In the moderate dose regimen, used in more major surgical procedures, an initial IV dose of *2–20 mic/kg* is administered, additional doses of *25–100 mic* may be given IV or IM as necessary. In the high dose regimen used in complicated procedures where surgery is more prolonged an initial IV dose of *20–50 mic/kg* may be given.

To provide general anesthesia without additional anesthetic agents, fentanyl doses of *50-100 mic/kg* may be administered IV in conjunction with oxygen and skeletal muscle relaxant.

Pethidine (Meperidine)

It produces a pattern of effect similar to that of morphine. The analgesic effect appears about 15 minutes after oral administration, reaches a peak in about 2 hours and subsides gradually over several hours. After parenteral administration peak effect appears in one hour. *Equianalgesic dose of IV pethidine is 100 mg to 10 mg of morphine (morphine is 10 times more potent).* Other more potent newer narcotics are Buprenorphine, Alfentanyl and Sufentanyl used mostly by anesthesiologist in the operation theatre.

Narcotic over dosage The standard reversal agent in the setting of opiate over dose is Naloxone, a competitive antagonist. *Dose of naloxone is 0.01 mg/kg IV slowly.* Rapid infusion can result in *withdrawal* seizures in patients receiving morphine on a chronic basis. The half-life of Naloxone is 45 minutes.

Ketamine

Ketamine hydrochloride is an Arylcycloalklyamine (a phencyclidine derivative). It induces a state of sedation, immobility, amnesia and marked analgesia. It induces dissociative anesthesia: Strong feeling of dissociation from the environment that is experienced by the patient to whom it is administered.[8] Ketamine has been extensively used in pediatric patients in radiology, burns dressings and other painful procedures. Ketamine is ideal sedative in a relatively hypovolemic patient, patient with bronchospasm, and shock due to its indirect sympathomimetic action by releasing catecholamines causing hypertension and bronchodilatation.

IV dose is 1 to 4.5 mg/kg over a period of about one minute. The sensation of dissociation is noticed within 15 seconds and unconsciousness becomes apparent within 30 seconds. Intense analgesia and amnesia are established rapidly. Following a single dose, unconsciousness lasts 10-15 minutes and analgesia persists for 40 minutes, amnesia may be evident for 1 to 2 hours following the initial injection.[8] If anesthesia of longer duration is required repeat dose equal to half of the initial dose may be administered. Muscle tone may be increased, purposeless movements may sometimes occur, and violent and irrational responses to stimuli occur. Pharyngeal and Laryngeal reflexes are retained and although cough reflex is depressed, airway obstruction does not normally occur. Airway resistance is decreased and bronchospasm may be abolished. Unlike barbiturates, ketamine does not act on reticular activating system, rather it acts on receptors in the cortex and limbic system. Awakening may be characterized by disagreeable dreams and even hallucinations. Some of these occurrences may occur days or weeks later. Avoiding exposure to bright light or loud noises following use of ketamine can reduce the emergence hallucinations. Concominant use of midazolam to reduce hallucinations is not proven therefore not necessary. Relative contradictions include known hypertension and raised intracranial pressure.

Propofol

Propofol (2,6-diisopropyl phenol) is an IV anesthetic which is given to critically ill children for titratable sedation and hypnosis. Propofol has a wide array of benefits, including anxiolysis, anticonvulsant activity, antiemesis, and the ability to reduce intracranial hypertension.[9,10] Similar to the benzodiazepines, propofol has no analgesic activity.[11] The most important advantage of propofol is its rapid onset and offset of action. This behavior of a "rapid on, rapid off" feature, not available with the IV opiates or benzodiazepines, accounts for the increasing popularity of propofol. Because the onset of action after a single dose is rapid, and its effect brief (10-15 minutes) due to high lipophilicity and central nervous system penetration, propofol is given only by continuous infusion when used for sedation.

The emergence from anesthesia is rapid even following prolonged infusion and is characterized by minimal postoperative confusion. Given in conjunction with diazepam or midazolam, propofol provides satisfactory anesthesia for a variety of purposes like emergency surgical procedures, change of dressings, radiological procedures and even some cardiac surgical procedures. The most significant adverse effect of propofol is hemodynamic destabilization. Propofol can substantially reduce cardiac output because it is both a negative inotrope and negative chronotrope. Additionally, it is a vasodilator. The combined effects on cardiac output and systemic vascular resistance can cause significant hypotension.[11] Pancreatitis, perhaps related to hypertriglyceridemia, has been described after the use of propofol.[12] It is a potent respiratory depressant, suppressing both the hypercarbic and hypoxemic drives of ventilation. Following induction of anesthesia, respiration is so depressed that apnea may occur for 30 seconds. Tidal volume, minute volume and functional residual capacity, all are subsequently reduced. It does not impair hepatic or renal function. Pain with peripheral injection has been described, therefore, central delivery routes are preferred. It is chemically unrelated to other IV anesthetic agents. *The compound is an oil at room temperature and supplied as 1 percent emulsion. An IV injection of 2 mg/kg induces anesthesia rapidly.*

Caution: In younger patients continuous infusion is to be discouraged due to recent reports of metabolic acidosis and cardiovascular collapse.

Chloral Hydrate

Chloral hydrate is used principally as an oral/rectal hypnotic in the treatment of insomnia. It is effective as hypnotic only for short term use. It may also be used as a routine oral sedative agent. The drug is used preoperatively to allay anxiety and produce sedation. In postoperative cases it may be a useful adjunct to opiates and analgesics.

It is also used for non-stimulating procedures requiring sedation only, e.g., prior to EEG.

Dosage[13] is the same for oral and rectal administration and must be individualized for each patient.

For children, the *hypnotic dosage of chloral hydrate is 50 mg/kg or 1.5 g/m^2 with a maximum single dose of 1 gm.*

The sedative dosage for children is 8.3 mg/kg or 250 mg/meter sq three times daily with maximum dosage of 500 mg 3 times a day. As a pre-medication before EEG, children have been given in a dose of 20-25 mg/kg. Toxicity can manifest as gastritis, Skin eruptions or parenchymatous renal damage may develop following prolonged administration of chloral hydrate. Prolonged use may also produce tolerance and physical dependence. Chloral hydrate overdosage produces symptoms which are similar to those of barbiturate overdosage like coma, hypotension, hypothermia, respiratory depression and cardiac arrhythmias. Miosis, vomiting, areflexia, muscle flaccidity, esophageal stricture, gastric necrosis, perforation and gastrointestinal hemorrhage have been reported.[13]

Treatment of chloral hydrate intoxication consists of general supportive therapy including maintenance of adequate airway, assisted respiration, oxygen administration and maintaining body temperature and circulation. Gastric lavage may be performed following over dosage if an endotracheal tube with cuff inflated is in place to prevent aspiration of gastric contents.[13]

Newer Agents

Two alpha-2 adrenergic agonists have recently been registered by US Food and Drug Administration, namely: *Clonidine and Dexmedetomidine.*

The alpha-2 adrenergic agonists provide analgesia, anxiolysis sedation and sympatholysis. Epidural clonidine was used as an adjunct for pain management particularly in patients with cancer.[14] Dexmedetomidine was approved for use as a sedative and analgesic in the intensive care setting specifically for use in early postoperative period.[15]

Dexmedetomidine is the first sedative with analgesic properties that does not significantly depress respiratory drive or produce respiratory depression. So it holds a promise in ICU of being a sedative analgesic without causing respiratory depression. It can be administered during and after extubation from ventilatory support. Patients are calm and easily arousable from sleep.

These agents cause bradycardia, by vagomimetic effect and blockade of cardio-accelerator nerve. They also cause hypotension due to inhibiton of sympathetic activity in the central nervous system leading to vasodilation.

PRACTICAL APPROACH TO SEDATION IN THE PICU

Sedation in children is usually performed with one or combination of benzodiazepines, opiates, neuroleptic agents and anesthetic agents such as propofol and ketamine. Each of these groups of medications has their particular benefits: benzodiazepines provide the greatest analgesia and propofol is the most easily titrable and has a more rapid reversal of sedation other than providing amnesia.

For short nonstimulating procedures requiring sedation only, chloral hydrate alone may be used.

All patients require sedation of some degree during mechanical ventilation.

There have been a number of studies published for the sedation of mechanically ventilated patients. The most important goal in the sedation of these patients is to achieve patient comfort and patient-ventilator synchrony to avoid any mishaps during ventilation such as accidental extubation, circuit disconnection or kinking of circuits.[16]

The basis for sedating these patients starts with an infusion of an opioid, usually morphine, or fentanyl. Fentanyl has the advantage of avoiding hypotension from histamine release.

Cost of fentanyl is higher compared to morphine. Once proper analgesia has been established, an infusion of a sedative should be added. The most popular sedatives at our institution are benzodiazepines, specifically midazolam.

If no painful procedures are contemplated midazolam infusion alone is sufficient. Ketamine or narcotic supplementation should be given before painful procedures such as central line, arterial line insertions and chest tube placement or chest physiotherapy. Older children require muscle relaxants in addition to sedation, especially in cases of acute respiratory distress syndrome or other low compliance lung disease.

It is important to remember that most common condition causing agitation in a child on ventilator is hypoxemia due to mechanical issues such as secretions, endotracheal tube misplacement, kink or pneumothorax. This must be addressed with adequate oxygen delivery, clearance of secretions, delivery of adequate tidal volume, ensuring proper placement of endotracheal tube, and treating pneumothorax as the case may be, before sedating the child for anxiolysis and comfort.

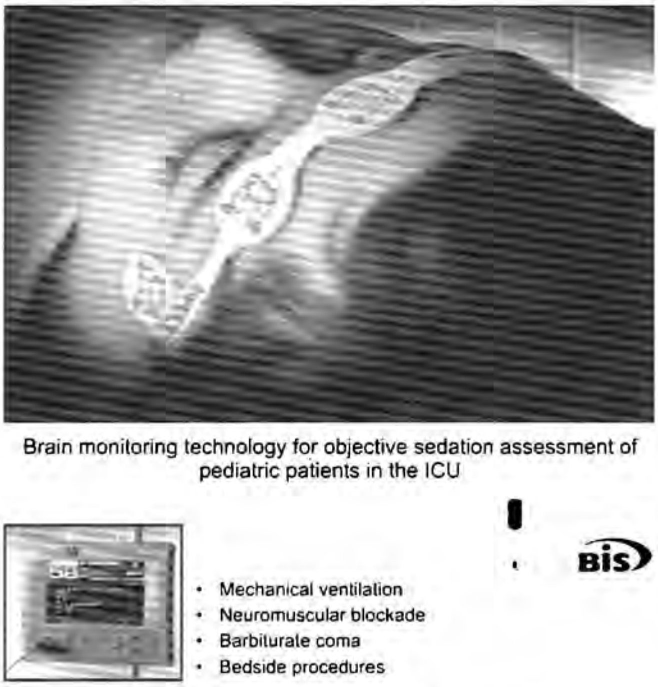
Brain monitoring technology for objective sedation assessment of pediatric patients in the ICU
BIS
Mechanical ventilation
Neuromuscular blockade
Barbiturate coma
Bedside procedures

Fig. 88.1: BIS scale in use with monitor

Newer developments Recently *bispectral index* (BIS) has been evaluated for monitoring of sedation/level in a muscle relaxed patient, it was found to correlate well with ramsay score (Fig. 88.1). The instrument consists of mini EEG monitor which leads strip is placed on the patients forehead (Aspect medical systems, inc. USA) and the sedative dose can be titrated.

The BIS score ranges from 0–100 and is a reliable index of the state of consciousness in normal subjects. Scores more than 95 indicate full consciousness. Of sedated patients, 95 percent are unconscious if the BIS score is 50.

Its use is mainly for patients without a neurological illness who are sedated due to being on a mechanical ventilator.

There are some preliminary reports on its use in the neonates. Unfortunately, the BIS score may be complicated if the EEG also reflects changes in the neurologic status of the patient that are caused by the illness itself.

SUMMARY

It is well documented that perception of pain in children is as much as in adults.[17] Though more difficult to manage compared to adults, it is mandatory to provide adequate comfort control measures to critically ill children.[18] The child also needs protection against the tremendous stress response and excessive motor activity resulting from the physiological stress of the illness and which may interfere with intensive care.[19] Failure to provide adequate sedation and analgesia to control the stress response has been seen to be associated with increased complications and mortality.[20]

We follow a practice of judicious use of sedatives in our PICU to try to make stressful and traumatic experience in PICU smoother for the child as well as for the parents. One must not forget to use analgesia where painful procedure is anticipated in a child. Availability of proper resuscitative equipment as well trained personnel is extremely important to ensure safety of the child during all procedures, specially those performed in radiology or endoscopy suites. Routine use of muscle relaxants can be avoided, to be reserved for mechanically ventilated patients with severe acute respiratory syndrome or raised intracranial tension.

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NEUROMUSCULAR BLOCKADE

In the PICU, neuromuscular blocking agents (NMBA) are frequently administered as a bolus to obtain rapid control of the airway, (e.g., during endotracheal intubation), to perform short procedures once the airway is secured, and analgesics administered, (e.g., pericardiocentesis, central line, thoracostomy tubes), or while transporting a patient to avoid accidental extubation. Neuromuscular blocking agents are also used as continuous infusions or at regular intervals in certain patients receiving mechanical ventilation, when interference with mechanical breaths may be harmful (e.g., risk for barotrauma, increased intracranial pressure). These agents do not have any analgesic or sedative properties and therefore, must always be used with concomitant analgesia and/or sedation. The ability to control airway and manually ventilate the patient must be assured as a prerequisite to administration of NMBA.

Goals

The response to NMBA is often unpredictable, therefore, clinical evaluation of satisfactory paralysis is more relevant than using a fixed dose. Satisfactory paralysis is dependent on the objectives, e.g., for intubation the mouth should be opened without difficulty, there should be no coughing, or movements of the vocal cords or the diaphragm; while for continuous ventilatory support, there should be no interference with mechanical breaths (fighting or bucking). All NMBA at equipotent doses will produce same neuromuscular effects.

Things to Consider when Choosing a NMBA

Speed of Onset

Rapid onset occurs when the drug induces paralysis in less than 1 min (Table 88.2). Some drugs can speed their onset when administered at larger doses, but their effects are prolonged. To speed up the onset, a priming principle can also be used. Priming principle is used to speed up the onset when using an intermediate or long-acting agent, but can be unpredictable in the PICU setting. One-tenth of the NDPA is given 4 min before a full dose. The small dose will saturate some receptors without producing paralysis. The second dose will act more rapidly because there are less receptors available, (e.g., Pancuronium 0.01 mg/kg followed 4 minutes later with Pancuronium 0.1 mg/kg). Other NMBA will take from 1-5 min to induce paralysis at regular doses IV. Rarely, they may be administered IM or sublingually in an emergency, but their onset is unpredictable.

Table 88.2: Drugs with rapid onset of action

Drugs	*Doses mg/kg*	*Recovery time*
Mivacurium	0.2-0.25	Within 20 min
Vecuronium	0.4	Within 90 min
Succinylcholine	1.5-2	5-10 min

Duration of Paralysis

Drugs are divided into short (approximately less than 20 min), intermediate (within 40 min.), and long-acting (close to 1 hr.) (Table 88.3). The duration of action may be influenced by the quantity administered and in some cases by the age of the patient. For drugs used for continuous infusion see Table 88.4.

Mechanism of Action

Succinylcholine is the only depolarizing agent available. It may have effects that are undesirable, and has specific contraindications (Table 88.5). All other NMBA are of nondepolarizing variety.

Table 88.3: Duration of action/doses in mg/kg

Short	*Intermediate*	*Long*
Mivacurium 0.2-0.25	Atracurium 0.4	Pancuronium 0.06-0.1
Succinylcholine 1.5-2	Vecuronium 0.1	Metocurine 0.2-0.3 Vecuronium* 0.1 Pipecuronium 0.5 d-Tubocurarine 0.2-0.6

Table 88.3: Duration of action/doses in mg/kg

Short	*Intermediate*	*Long*
Mivacurium 0.2-0.25	Atracurium 0.4	Pancuronium 0.06-0.1
Succinylcholine 1.5-2	Vecuronium 0.1	Metocurine 0.2-0.3 Vecuronium 0.1 Pipecuronium 0.5 d-Tubocurarine 0.2-0.6

Table 88.4: Drugs for continuous infusion

Drug	*Initial bolus mg/kg*	*Infusion mg/kg/hr*
Atracurium	0.15-0.25	0.5-0.6 (In liver renal failure a metabolite laudanosine may cause CNS stimulation)
Vecuronium	0.1	0.1-0.15 (Prolonged effets in renal and liver failure)
Mivacurium	0.1	0.7-0.9 Limited data

Table 88.5: Contraindications of succinylcholine

Burns: 3 days to 6 months
Massive trauma 3 days to 1 year
Stroke/paraplegia 3 days to 1 year
Myotonias
Duchennes muscular dystrophy
Fredriechs ataxia
Amyotropic lateral sclerosis
Multiple sclerosis
Guillain-Barré syndrome,
Spinal cord injury,
Penetrating injury to the ocular globe,
History of malignant hyperthermia,
Increased intracranial pressure
Chronic renal failure
Hyperkalemia
Expect prolonged effects in hepatic failure, malnutrition, pseudocholinesterase deficiency and hypermagnesemia.

Patient condition or drug interactions: That may affect the NMBA's effect, elimination, or transformation (Table 88.6).

Side Effects

Some drugs will produce a histamine release affecting the cardiovascular function, causing bronchospasm.

Table 88.6: Conditions or drug interactions that may affect the use of NDPA

Delayed onset and/or increased resistance
- Hyperkalemia
- Alkalosis
- Motor neuron lesions
- Burns
- Cerebral palsy
- Malignant abdominal, bone, or cerebral tumors
- Phenytoin (doses 3 times larger are needed)
- Carbamazepine

Increased sensitivity and/or delayed recovery
- Decrease in serum Na, K and Ca
- Hypermagnesemia
- Hypothermia
- Acidosis
- Administration of aminoglycosides
- Vancomycin
- Clindamycin
- Local anesthetics
- High-dose steroids
- Beta-blockers
- Calcium channel blockers
- Cyclosporine
- Potent inhaled anesthetics
- Myasthenia gravis.

Physiology of the Neuromuscular Junction

When an electrical nerve impulse reaches the neuromuscular junction, the release of acetylcholine (ACh) from the pre-synaptic neural terminal is triggered. Acetylcholine travels across the synaptic space to bind to ACh receptors on the post-synaptic membrane. These receptors function as tunnels between the intracellular and extracellular space. The binding of ACh opens these tunnels allowing the entry of Na and Ca and the release of K from the intracellular to the extracellular compartment. This creates changes in the electrical potential of the membrane at the neuromuscular junction resulting in a muscular contraction. Acetylcholine is rapidly hydrolyzed by plasma cholinesterase and rendered ineffective, thus closing the tunnel.

Non-depolarizing agents (NDPA) block the ACh receptors. Therefore, ACh cannot trigger the contraction. This mechanism of action is called competitive antagonism. Because binding of NDPA is reversible, when sufficient ACh is available, it displaces NDPA from the receptors restoring the neuromuscular transmission. By inhibiting the enzyme that degrades ACh (ACh-esterase), physostigmine, neostigmine or edrophonium produce an accumulation of a large amount of ACh reversing this blockade. The depolarizing agent, succinyl choline, binds to receptors (tunnels) mimicking ACh and producing a muscle contraction (usually seen as muscle fasciculations). This mechanism is described as competitive agonism. However, succinylcholine does not undergo rapid enzymatic degradation by cholinesterase and the membrane remains depolarized (the tunnel remains open) producing flaccid paralysis. After a few minutes, succinylcholine diffuses away from the receptor and sufficient ACh builds up producing a reversal of paralysis. Receptors of the neuromuscular junction are classified as nicotinic, but acetylcholine binds also to muscarinic receptors on autonomic ganglia. When larger amounts of ACh are present in muscarinic receptors (when ACh-esterase is inhibited), or when muscarinic receptors are stimulated by ACh like substances (e.g., Succinyl choline), bradycardia, excessive secretion, and bronchospasm may occur. The stimulation of muscarinic receptors in infants and children in whom a vagal tone predominates can lead to severe bradycardia. Therefore, muscarinic anticholinergics such as atropine or glycopyrrolate are used when these unwanted effects are anticipated. Infants have larger volumes of distribution than older children, and may require larger doses as mg/kg, but doses calculated per meter square are in general the same. The doses utilized in the PICU are higher than the ones used in the anesthesia setting when there is simultaneous use of potent inhaled anesthetics.

Monitoring Adequacy or Depth of Muscular Blockade

Good intubation conditions can generally be assessed by clinical evaluation. When prolonged muscle relaxation is the objective, a nerve stimulator that produces a Train of Four (TOF) is utilized. After placing two electrodes on the antero/exterior part of the distal third of the forearm, two electrical stimuli per second for two seconds are delivered to the ulnar nerve. The normal response is four twitches of the thumb with fairly similar amplitude. The fourth twitch disappears with 75 percent of the receptors blocked, the third with 80 percent, the second with 90 percent and all the twitches disappear with 100 percent of the receptors blocked. For prolonged mechanical ventilation 75-90 percent of blockade is usually accepted as satisfactory. In order to extubate a patient, a sustained head lift for 5 sec or a TOF with 4 twitches, suggest enough muscle strength for airway protection.

NON-DEPOLARIZING AGENTS

Short-acting

Mivacurium (Mivacron)

Mivacurium at 0.2-0.25 mg/kg intravenously (IV) may allow intubation within 1 minute (comparable to succinyl-choline), with recovery in 20 minutes. It is metabolized by plasma cholinesterase. Action will be prolonged in the presence of atypical plasma cholinesterase or acquired defects in plasma cholinesterase activity such as severe renal or liver disease (same as succinylcholine). It causes some histamine release. Typical uses are: rapid sequence intubation or laryngospasm.

Intermediate-acting

Vecuronium (Norcuron)

Vecuronium at 0.1 mg/kg IV takes 1.5 minutes to reach intubation conditions and recovery is expected within 20 minutes. At 0.4 mg/kg the onset is shortened to less than 30 sec., but recovery is within 90 min. In neonates and infants it is a rather long-acting agent. It is mainly excreted by the liver. A metabolite (3-dose acetyl vecuronium) does accumulate in renal failure prolonging the paralysis. It has the advantage being cardiostable and it does not cause tachycardia.

Atracurium (Tracurium)

Atracurium at 0.4 mg/kg IV produces paralysis within 2 min and recovery within 30 min. It undergoes ester (non enzymatic) hydrolysis and Hoffman degradation which is independent of hepatic and liver function, but a metabolite (Laudanosine) can accumulate that may produce CNS stimulation. It produces some histamine release particularly with higher doses, causing bronchospasm or hyperotension.

Long-acting Nondepolarizing Muscle Relaxants

Pancuronium (Pavulon)

Pancuronium at 0.06-0.1 mg/kg IV produces paralysis within 3 min. and time of recovery is about 1 hr. It is eliminated primarily by the kidney and renal failure can markedly prolong its effect. In hepatic failure, resistance to the drug and prolonged elimination has been described. Tachycardia and hypertension are common side effects.

Metocurine (Metubine)

The dose of metocurine is 0.2-0.3 mg/kg IV. Its action and elimination is fairly similar to pancuronium except that it does not have cardiovascular side effects.

d-Tubocurarine

d-Tubocurarine produces paralysis at a dose of 0.2-0.6 mg/kg IV. There is great variability on its effects and careful titration is needed. In hepatic failure there is a resistance to the drug. It produces histamine release, vasodilation with hypotension, bronchospasm and rash. It is not used in the PICU due to availability of newer safer agents.

Pipecuronium (Arduan)

Pipecuronium the dose is 0.5 mg/kg IV. Action may be similar to pancuronium, but there is insufficient pediatric data. Similarly alcuronium: (Alloferin) is available and the dose is 0.3 mg/kg IV. Its action is similar to pancuronium.

Reversal of NDPA

When there is residual paralysis secondary to a NDPA, it is possible to antagonize their effects (e.g. for extubation). In order to attempt this, there should be less than 90 percent of the receptors blocked (at least one contraction of the TOF).

Neostigmine 0.05-7 mg/kg or edrophonium 1 mg/kg combined with atropine 0.02 mg/kg or glycopyrrolate 0.01 mg/kg are used for this purpose and reversal occurs within 10 min.

Depolarizing Agents

Succinylcholine

Neonates and infants are given succinylcholine in doses of 2-3 mg/kg, children are given 1-2 mg/kg IV. Onset is within 1 minute and its duration is 5-10 min. It should be used with atropine 0.02 mg/kg or glycopyrrolate 0.01 mg/kg in young children. It can be administered IM; the dose should be doubled and the onset is delayed. It is metabolized by plasma ACh-esterase and some disease states may produce prolonged paralysis (see mivacurium). It produces an elevation of serum K (0.5-1 mEq/l). In conditions where there is massive tissue destruction or central nervous system injury with muscle wasting, it may lead to life-threatening hyperkalemia. This risk may persist for several months after an episode. It increases intraocular pressure and is associated with masseter spasm and malignant hyperthermia in special circumstances (Table 88.5). In patients with myasthenia gravis there is a resistance to succinylcholine. Typical uses are in cases of laryngospasm or rapid sequence intubation.

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CHAPTER

89

Hydrocephalus

Sandeep Chopra, Manish Vaish, Praveen Khilnani

Hydrocephalus is a fairly common problem in infants and children as newer advances in neonatology have led to increased survival of very low birth weight premature babies. These infants frequently require neurosurgical interventions for adequate drainage of the cerebrospinal fluid (CSF) causing raised intracranial pressure and complications thereof.

Management of an infant or a child in the immediate postoperative period after a ventriculoperitoneal shunt or ventriculostomy operation in the pediatric intensive care unit is an important issue. However early diagnosis and management of problems related to an obstructed or infected shunt that is already in place can be challenging. This chapter is intended to give basic guidelines for diagnosis and management of hydrocephalus in infants and children and issues related to ventriculoperitoneal shunts.

CSF Production and Physiology

A brief overview of CSF physiology is important to understand the management strategies related to increase CSF pressure leading to ventricular enlargement and enlargement of the head.

CSF is a mixture of secretion of choroid plexus plus interstitial fluid derived from parenchymal capillaries and cellular metabolic process.

In normal conditions about 60 percent of CSF is produced by choroid plexus, located in wall of ventricular system. Rest is secreted by metabolic water and capillary ultra filtrate. The net osmotic gradient across the choroid plexus is tightly regulated by the transport of Na^+, Cl^- and HCO_3.

CSF Hydrodynamics

CSF is formed at hydrostatic head of 15 mm of H_2O.

It is propagated through the pulsation of choroid plexus which is in turn due to pulsation of arteries in it. The pressure of CSF column is (100 to 180 mm of H_2O) 10-12 mmHg by lumbar puncture. At 10-12 mm Hg (112 mm of H_2O) the rate of production filtration and absorption are equal. At a pressure below 68 mm of H_2O the absorption stops. Choroid plexus of lateral ventricle is the largest and contributes to 60 percent CSF production.

CSF Functions

CSF function include

1. Support cushion countering traumatic effect by reduction of brain weight by 96 percent.
2. Ventriculo-cisternal bulk flow provides an alternate pathway for ions, molecules proteins and micro nutrients such as nucleosides and growth factors.
3. Clearing of waste as protein, metabolites, toxin, drug.
4. Integration of brain and peripheral enviornment

The CSF pathway is shown in Figure 89.1.

Absorption of CSF from subarachnoid space to arachnoid villi depends upon pressure differential between the subarachnoid space and intraluminal pressure in dural sinuses.

Different components of the CSF are absorbed at differential rate by different structures:

a. Water → Intravascular equilibrium of hydrostatic and osmotic pressure
b. Na^+ → Convexity veins

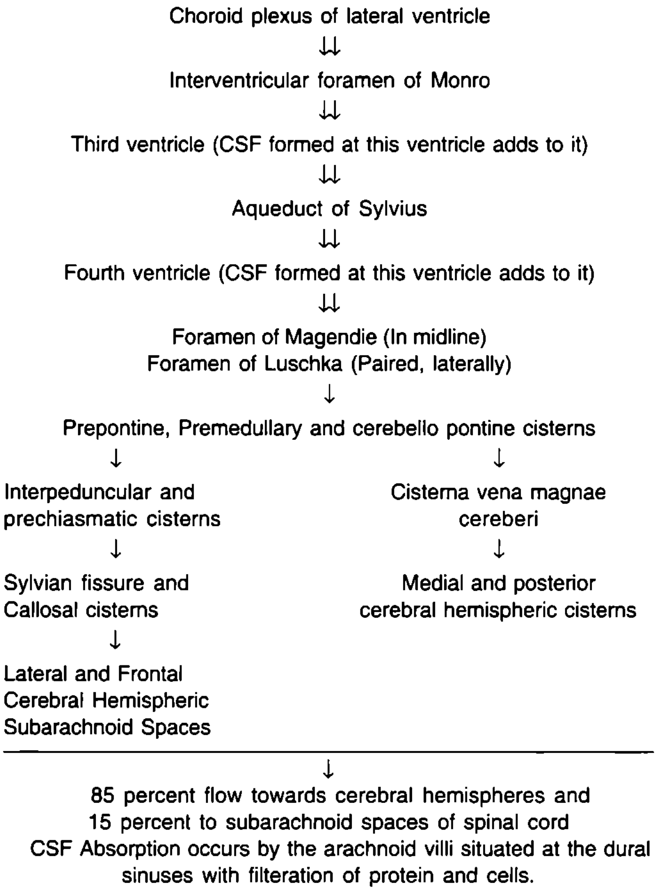
Choroid plexus of lateral ventricle
Interventricular foramen of Monro
Third ventricle (CSF formed at this ventricle adds to it)
Aqueduct of Sylvius
Fourth ventricle (CSF formed at this ventricle adds to it)
Foramen of Magendie (In midline)
Foramen of Luschka (Paired, laterally)
Prepontine, Premedullary and cerebello pontine cisterns
Interpeduncular and prechiasmatic cisterns
Cisterna vena magnae cereberi
Sylvian fissure and Callosal cisterns
Medial and posterior cerebral hemispheric cisterns
Lateral and Frontal Cerebral Hemispheric Subarachnoid Spaces
85 percent flow towards cerebral hemispheres and
15 percent to subarachnoid spaces of spinal cord
CSF Absorption occurs by the arachnoid villi situated at the dural sinuses with filteration of protein and cells.

Fig. 89.1: Flow pathway of CSF

c. Albumin → Sagittal sinus

d. Metabolites → Subarachnoid space but not from parenchyma to ventricular system.

Hydrocephalus

Imbalance in CSF formation and absorption of sufficient magnitude to produce net accumulation of fluid within cerebral ventricles leads to progressive enlargement of ventricles leading to the enlargement of head.

Hypothetically three mechanisms are described (Millohart et al):

i. Obstruction of the CSF pathway
ii. Over secretion of the CSF
iii. Impaired ventricular drainage.

Obstruction of CSF Pathway

a. More specifically obstruction proximal to the outlet foramina of 4th ventricle also called ***interventricular obstructive hydrocephalus (IVOH)*** or *noncommunicating hydrocephalus.*

b. Obstruction distal to foramina of 4th ventricle also called *extraventricular obstructive hydrocephalus (EVOH)* or *communicating hydrocephalus.*

Various causes of hydrocephalus are shown in Table 89.1.

Chronic Hydrocephalus

1. *Pathophysiology* Due to compensatory physiological adjustment there are following changes.
   a. Expansion of skull (if cranial sutures are open)
   b. Contraction of cerebral vascular volume and alteration in cerebral blood flow
   c. Volumetric enlargement of ventricular systems
   d. Decreased rate of CSF production
   e. Transventricular absorption
2. *Pathologic effects of chronic ventricular enlargement*
   a. Atrophy of white matter
   b. Periventricular spongy edema of brain

Table 89.1: Etiology of hydrocephalus

Causes of Interventricular obstructive hydrocephalus (IVOH) or Noncommunicating hydrocephalus

Congenital: 1. Aqueductal obstruction (stenosis)
- Gliosis
- Forking
- True narrowing
- Septum

2. Atresia of foramina of Luschka/Magnedie,
- Dandy Walker malformation

3. Masses
- Benign intracranial cyst
- Vascular Malformation
- Tumor

Acquired: 1. Aqueductal stenosis (gliosis)
2. Ventricular inflammation
3. Tumor and nonneoplastic masses

Causes of Extraventricular obstructive hydrocephalus (EVOH) or Communicating hydrocephalus.

Congenital: 1. Arnold Chiari malformation
- Encephalocele
- Leptomeningeal inflammation
- Lissen cephaly
- Congenital absence of arachnoid granulation

Acquired: 1. Leptomeningeal inflammation
- Infection
- Hemorrhage
- Particulate matter
- Masses
- Platybasia

Overproduction
Choroid plexus papilloma

c. Choroid plexus fibrosis
d. Stretching and denuding of ependymal surface
e. Ventricular diverticulas
f. Fenestration of septum pellucidum
g. Thinning and elongation of interhemispheric commisure

Acute Hydrocephalus

In acute hydrocephalus process of ventricular enlargement is not uniform. It starts from lateral ventricle and enlarged downward in following sequence until site of obstruction is reached.

In lateral ventricle the frontal horn and occipital horn dilate first, thereafter transverse dilatation of 3rd ventricle occurs and lastly 4th ventricle dilates posteriorly into the cerebellum.

There is acute increase in first 3-6 hours, after 6 hours there is slowing of enlargement due to (a) easily available space being already consumed and (b) compensatory mechanisms come in to action. After 3 hours the chronic changes start.

Clinical Features

Infants

1. Rapid head enlargement
2. Craniofacial disproportion, i.e. enlarged dome and low set ears and eyes
3. Thin and glistening scalp
4. Anterior fontanelle becomes tense and bulging, without pulsation
5. Scalp veins fails to collapse
6. Percussion of head elicits Macewen's sign
7. Trans illumination test is positive in infants with skull thickness less than 1 cm.
8. *Sunset sign:* downward angulation of the eye balls with iris half visible.

Older Child

1. *Acute:*
   i. Nausea, vomiting, headache due to rapid and severe ICP
   ii. Episodes of transient/permanent blindness due to trans tentorial herniation and entrapment of PCA against free edge of tonsil.
   iii. Parinaud's syndrome, due to dilatation of supra pineal recess which presses against quadrigeminal plate
   iv. Absence of central retinal vein pulsation
   v. 3rd and 6th nerve palsy.
2. *Chronic:*
   i. Bifrontal or generalised headache
   ii. Vomiting
   iii. Papilledema or optic atrophy
   iv. Failing mental function
   v. Behavioral disturbances
   vi. Memory loss.

   Unilateral or bilateral 6th nerve palsy.

Diagnosis

CT scan/MRI of the brain is helpful for precise diagnosis.

IVOH

Following features are seen on CT/MRI:

1. Size of both temporal horn greater than or equal to 2 mm with effacement of sylvian and intrahemispheric fissure.
2. Effacement of sylvian sulci.
3. Ballooning of frontal horn and 3rd ventricle.
4. Periventricular low density on CT and Periventicular high signal intensity on T2W images on MRI.
5. Evan's ratio (frontal horn/maximal biparietal distance) greater than 30 percent.
6. Saggital MRI shows upward bowing of corpus callosum and obliteration of collateral sulcus.

Management of Hydrocephalus

Principles

1. *Excision of obstructive lesion:* Posterior fossa tumors, occupy about 2/3 of posterior fossa.

   Neurosurgical management usually does not require shunt placement after removal of the tumor.
2. *Indications and contraindications for CSF shunt insertion*

   Indications
   a. Signs and syptoms of raused ICP in setting of hydrocephalus
   b. Relieving the pressure following tumor removal
   c. Communicating hydrocephalus.

Contraindications

Following are absolute contraindications:

a. Ventriculitis
b. Acute intraventricular hemorrhage (Contusions).

Relative Contraindications

a. Hydrocephalus with untreated obstructive lesion.
b. Futility on the basis of extreme brain pathology, i.e. hydranan cephaly.
c. Asymptomatic, nonprogressive hydrocephalus.
d. Ventriculomegaly without elevation of ICP.

Options for CSF drainage procedure:

A. 1. Ventriculoperitoneal (VP) shunt
   2. Ventriculoatrial shunt
   3. Ventriculo pleural shunt
   4. LP shunt in cases of communication hydrocephalus

B. 1. Endoscopic 3rd ventriculostomy
   2. Endoscopic aqueductoplasty

Postoperative care after a shunt placement involves close monitoring of the infants cardiorespiratory status, analgesia, monitoring for signs of shunt malfunction, bleeding, or signs of raised intracranial pressure. Rarely episodes of apnea, irregular breathing, hemodynamic instability, lethargy, hypertension and bradycardia may require reoperation indicating clot/obstruction of the shunt. Most patients will just need over night observation in the pediatric intensive care unit.

Long-term Problems with Ventriculoperitoneal Shunts

Shunt Obstruction and Infection

Any infant with a ventriculoperitoneal shunt can present with fever, irritability, poor feeding, vomiting and increasing head circumference. Enlarging head circumference and sunset sign in the patient with a shunt should be treated as emergency and an evaluation for shunt function must be done, as this situation can deteriorate into lethargy, seizures, coma and herniation. Shunt infection and obstruction go hand in hand in most situations. Clinically examination of shunt valve (felt subcutaneously in scalp) will usually depict obstruction. There is no refill of the valve after application of finger pressure used to empty it. A neurosurgical consult is warranted. *CT scan* of the head is indicated. A *shunt tap* may be required to document infection. CSF examination will reveal cloudy fluid with elevated protein, low glucose and elevated white cell count indicating evidence of meningitis/ventriculitis. A Gram stain may be helpful to initially guide the empirical antibiotic therapy pending final cuture results.

Treatment

Treatment of shunt infection invariably involves removal of shunt and a placement of ventriculostomy drainage to prevent raised intracranial pressure. Antibiotics of choice usually should include staph coverage and an adequate gram negative coverage, Ceftriaxone and vancomycin may be good initial coverage, but final culture and sensitivity of the CSF will determine the choice of antibiotics in the Indian settings, *Staphylococcus*, Pseudomonas, and Klebsiella are common causative organisms.

New shunt placement is usually not advised until meningitis has been treated adequately. In infants with gram negative meningitis, a minimum of 21 days of intravenous antibiotics may be required. Nevertheless negative CSF cultures and improving CSF biochemistry and cellular picture is a prerequisite for shunt revision.

Other common problem that is seen is increase in the length of the child leading to outgrowing of the shunt size. This may need shunt revision.

SUMMARY

Hydrocephalus is an important neonatal and pediatric problem requiring serious attention to avert a preventable morbidity and mortality. Patient with a shunt with fever, irritability, poor feeding, lethargy or any neurological symptoms should be presumed to have shunt problem, with or without head enlargement (obstruction, infection or both) until unless proved otherwise.

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CHAPTER

Status Epilepticus

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Status epilepticus (SE) is a neurological emergency. It is defined by the International League Against Epilepsy as "Epileptic seizures that are so frequently repeated, or so prolonged as to create a fixed and lasting epileptic condition."[1] In practical terms, it consists of a series of seizures without recovery of consciousness in the interim, or one prolonged seizure of more than thirty minutes duration. Practically speaking most seizures resolve within a few minutes, so seizures persisting for longer than 5 to 7 minutes should probably be treated as SE. Uncontrolled SE may lead to significant morbidity and mortality. A third of all deaths from epilepsy are related to status. The purpose of this chapter is to provide a practical overview and specific strategies in management of a critically ill child with SE in the emergency room and the pediatric intensive care unit (PICU).

Incidence

Three percent of all non-neurological admissions to the intensive care unit showed SE. SE is seen in 9 percent of patients with symptomatic epilepsy, and in 1.6 percent of patients with idiopathic epilepsy.[2]

Exact Indian figure regarding the incidence of SE are not available. Lacroix et al[3] reported the incidence of SE as 1.6 percent of all admissions to the PICU, 50 percent of these were children below 2 years of age, resulting in 6 percent mortality in the PICU and 9 percent at one year follow-up after discharge. In this study 32 percent patients had epilepsy, 13.6 percent had atypical febrile convulsions, 13 percent had purulent meningitis and 13 percent had encephalitis. In 1.3 to 5 percent patients other causes such as intoxication, tumor, recent anoxic encephalopathy, systemic hypertensive crisis, acute or chronic metabolic encephalopathy were seen.

Table 90.1 shows the clinical classification of SE. Generalized tonic-clonic status is the most common form, and also the one with the highest mortality and morbidity. Tonic status is less common. Clonic status is generally seen in infants and young children. Some neonates may manifest electrical status epilepticus without any overt clinical seizure activity.

Table 90.1: Clinical classification of SE

Genralized convulsive status epilepticus (GCSE)
- Primary generalized SE
- Tonic-clonic SE
- Myoclonic SE
- Clonic-tonic-clonic SE

Secondary generalized SE
- Partial seizures with secondary generalization
- Tonic SE

Non-convulsive status epilepticus (NCSE)
- Absence status (petit mal)
- Atypical absence status
- Atonic SE
- NCSE as a sequel to partially treated GCSE

Partial SE
Simple partial SE
- Typical
- Epilepsia partialis continua (EPC)

Complex partial SE (CPSE)
Neonatal status epilepticus

In neonates with altered mental status EEG should be performed to detect nonconvulsive seizure activity.[4,5]

Pathophysiology

Status epilepticus is associated with the development of sustained, high frequency epileptiform discharges on the electroencephalogram (EEG). These discharges may be widespread, or localized over a small area of the scalp. At the same time, there is an increase in the systolic blood pressure and cerebral blood flow. The cerebral metabolic rate of utilization of oxygen (CMRO$_2$) increases 300-400 percent. Lactic acid accumulates both in the blood and in the brain.[6] The cerebral cortex also shows accumulation of arachidonic acid, prostaglandins, and leukotrienes. In turn, these agents lead to cellular edema and cell death. Accumulation of excitotoxins like aspartate and glutamate in the extracellular spaces is also noted, and plays a major role in triggering calcium-mediated cell damage. In addition oxygen free radicals,nitric oxide are released. These agents are toxic to phosphorylation process of enzymes leading to inadequate ATP production. This further contributes to cellular edema and damage due to altered cell membrane permeability.

Neuronal injury from the above mechanisms becomes apparent in experimental status epilepticus after 30 minutes of seizure activity (the "transitional period"), even in adequately ventilated and oxygenated animals. The longer the duration of status, the more difficult it becomes to control.[7] Hyperpyrexia from the excessive muscle contraction may also cause neuronal injury. The excessive skeletal muscle contraction may lead to myoglobinemia and myoglobinuria. Cardiac dysrhythmias, aspiration pneumonia and sudden death may also occur during the course of the seizure. Combined respiratory and metabolic acidosis with hyperglycemia is common. Hyperkalemia may also be seen as a result of shift of intracellular potassium to extracellular space in response to acidosis.

In a study of immature (4-day-old) rats, a single, two hours episode of status epilepticus induced by fluroethyl compound irreversibly curtailed growth in brain weight and brain DNA synthesis.[8] The animals subsequently also showed delayed behavioral milestones and reduced seizure thresholds. It is conceivable that even in the human neonate, serial seizures permanently impair brain development. Here in lies the urgency to control the seizure activity promptly.

Etiology

Hypoxicischemic encephalopathy, cerebral infarction, intracranial hemorrhage (subarachnoid/ intra parenchymal/intraventricular), bacterial meningitis, viral encephalitis, and congenital central nervous system malformations, e.g. hydranencephaly/porencephaly are common etiological factors in neonates. In addition hypoglycemia, hypocalcemia, hyponatremia, and hypomagnesemia are commonly seen in the neonatal age group.

Status epilepticus of infants and children can be subdivided into the idiopathic and symptomatic groups. A clearly definable neurologic deficit is present in the latter category, e.g. mental retardation, and microcephaly. An etiology (e.g., bacterial meningitis, herpes, Japanese B encephalitis, cerebral malaria or head trauma) is also identifiable in the symptomatic category. Idiopathic status is easier to control than the symptomatic status.

Most common precipitants of status epilepticus in infancy and childhood are febrile illnesses and subtherapeutic serum anticonvulsant levels, the latter being observed in child with previously diagnosed and treated epilepsy (commonly from non-compliance/inadequate dosing/impaired gastro-intestinal absorption due to gastroenteritis/ accelerated systemic clearance in fever). Head injury, central nervous system infections, hypoglycemia or hyponatremia can also provoke status epilepticus. In western set up N acetyl cysteine therapy, camphor poisoning, cocaine abuse, tricyclic intoxication, cat scrach disease should also be considered. Hypocalcemia rarely triggers seizures outside of the neonatal period. Rare causes such as theophylline toxicity, hypertensive crisis and thyrotoxicosis should also be considered as important causes of SE.

Clinical Features

Obviously, convulsive status epilepticus is easy to recognize. Infants tend to have single prolonged seizure, rather than series of small, frequent seizures.

The patient may have associated respiratory compromise, urinary incontinence, sweating, or fever. Patients with non-convulsive status epilepticus (NCSE) (absence or complex partial type) usually present with stupor or confusion. Absence status epilepticus is characterized by a continuously uniform state of unresponsiveness. Patients with partial complex seizure status have a fluctuating sensorium, with periods of staring and unresponsiveness alternating with periods of automatisms during which the patient is somewhat responsive. The impairment of consciousness is due to epileptogenic paroxysms involving the amygdala and hippocampus on both sides, and/or deeper subcortical structures.[9] Tonic head and eye deviation to one side, nystagmus, and mutism may also be seen in complex partial status.

Status epilepticus is difficult to recognize in the critically ill patients who are pharmacologically muscle relaxed and mechanically ventilated. A high index of suspicion is necessary in such instances. EEG studies help confirm the diagnosis in muscle relaxed patients and in those with NCSE, demonstrating continuous spike/spike-wave patterns over a focal or a generalized distribution.[10] Most patients with SE will have eye opening within 20 minutes of abolishion of seizures (postictal drowsiness). Patients who do not wake up in this time period, therefore, should be considered to have NCSE, subjected to EEG and should receive anticonvulsant therapy to control NCSE.

Differential Diagnosis

Patients with tetanus may have tonic spasms of various segments of the body. Consciousness remains preserved during these attacks, and there is no accompanying nystagmus. Psychogenic seizures should be considered in patients with bizarre, out-of-phase flinging motions of the body which fail to respond to adequate anticonvulsant therapy. Patients with oculogyric crises, e.g. due to phenothiazine ingestion, may have painful, tonic upward deviation of the eyes, but sensorium remains preserved during these attacks. A urine toxic screen also helps confirm the diagnosis. In rare instances, electroencephalographic and video-electroencephalographic telemetry studies are needed to rule-out the above disorders.

Laboratory Investigations

The following investigations are generally recommended:

1. *CBC (complete blood count) and Serum electrolytes,* glucose, bloodurea nitrogen in all patients, with the addition of calcium and magnesium in neonates.
2. *Serum anticonvulsant levels:* In anyone with a known prior epilepsy.
3. *Lumbar puncture (LP):* LP may be performed after achieving seizure control, in febrile patients not manifesting signs of increased intracranial pressure, in order to exclude bacterial meningitis, viral encephalitis or subarachnoid hemorrhage. As a rule CT (computerized tomography) scan of head should be obtained before LP if any focal deficit, unequal pupils or SE is encountered. Patients with typical febrile seizures do not require a CT before LP if no focal deficit is found and there is strong suspicion of bacteremia and meningitis on clinical examination and CBC determination.
4. *Non-contrast head CT scan*: In patients with focal findings, head trauma, stupor or coma lasting more than 3-4 hours, in order to exclude cerebral contusion, infarction, subarachnoid hemorrhage, brain abscess, acute epidural or subdural hemorrhage. MRI (Magnetic resonance imaging) scan with and without contrast is preferable after the patient has been stabilized for better resolution of subtle lesions and depiction of meningeal enhancement with contrast in patients with suspected meningoencephalitis.
5. *Arterial blood gases*: To monitor for acidosis, hypoxia and hypercarbia.
6. *Urine for myoglobin*: In patients with prolonged convulsive status.
7. *Toxicology*: Urine drug screens (if available) in patients with suspected drug ingestion e.g., tricyclic ingestion, serum theophylline levels in those taking this drug.
8. *Electroencephalogram (EEG):* To help diagnose non-convulsive status epilepticus (NCSE), and in the muscle relaxed and mechanically ventilated patient treated for SE.

In the neonates with seizures and metabolic acidosis further metabolic work up for organic acidemias or aminoacidurias may be required.

TREATMENT OF STATUS EPILEPTICUS

As in any medical emergency, a team approach is suggested. The team leader should have a clear grasp of investigations that are required, general supportive measures, as well as specific anticonvulsant therapeutic measures, and should communicate these succinctly to other members of the team. The team leader should also have thought out, what the next management step will be in case of failure of the therapeutic measure being applied at a given juncture.

Close EEG monitoring may be necessary in neonatal status, as well as in those instances where the patient is pharmacologically muscle relaxed.

Diagnosis and treatment of the underlying encephalopathy should proceed simultaneously with efforts at controlling the seizure activity, e.g. antibiotics for bacterial meningitis, acyclovir for suspected herpes encephalitis, and mannitol for cerebral edema. Mild peripheral leukocytosis of less than 18,000 to 20,000/c.mm, and mild cerebrospinal fluid pleocytosis (5-15 WBC/c.mm) may occur as a consequence of the status epilepticus *per se*.

Immediate Resuscitative Measures in the Emergency Room (ER)

Provision of 100 percent oxygen by mask during the seizure, emergency endotracheal intubation may be necessary if seizure is longer than 10 minutes despite initial anticonvulsive therapy. Hypoxia and hypotension should be prevented at all costs. 1 ml/kg of 50 percent extrose may be given in emergency if blood sugar is not readily available.

General supportive measures include judicious (not overzealous) suctioning of the oropharynx, placement of a nasogastric tube followed by aspiration of the gastric contents, and administration intravenous fluids if hypotension is encountered. Inotropic support with dopamine may be necessary for hypotension unresponsive to fluid administration. Hyponatremia, hypocalcemia, hypoglycemia and hypomagnesemia, if present, should be corrected.

Anticonvulsants These agents are needed if seizures are occurring in the absence of a promptly correctable disorder like hypoglycemia, hypocalcemia, or hyponatremia. Once a seizure has been observed to continue for more than three minutes, intravenous anticonvulsants should be administerd.[11] The anticonvulsant should be administered via the intravenous route, and in a dose large enough to produce an immediate therapeutic serum level. An important therapeutic concern is the rapidity of onset of action of the drug. Diazepam and lorazepam have onset of action within 1-2 minutes, phenytoin within 10-15 minutes, and phenobarbital within 20-30 minutes. Since diazepam is rapidly redistributed, the duration of its-anticonvulsant action is, however, only about 15 minutes. On the other hand, lorazepam has an anticonvulsant effect lasting 4-6 hours. For both phenobarbital and phenytoin, the free (unbound) fraction is about one-tenth of the total serum level. It is only this unbound fraction that crosses the blood-brain barrier. The greater the peak serum level, the greater the amount of anticonvulsant diffusion into the brain. For prehospital treatment rectal diazepam or rectal/nasal midazolam (0.05 to 0.34 mg/kg) can be used.Rectal diazepam (0.4 to 0.5 mg/kg) has been shown to lead to lesser chances of later endotracheal intubation compared to intravenous diazepam.[12]

Anticonvulsant Therapy for SE

Intravenous (IV) lorazepam[13,14] should be administered, in a dose of 0.05-0.15 mg/kg, to a maximum of 2 mg slow IV. One may repeat the dose two more times at 10-20 minute intervals. Lorazepam is most effective in status epilepticus that is not associated with acute structural lesions.[15] In one study with the use of lorazepam, chances of endotracheal intubation were significantly less when compared to patients who received diazepam.[16] If lorazepam is unavailable, diazepam, 0.2-0.3 mg/kg may be administered. The dose may be repeated twice at 10 minute intervals, if necessary. As diazepam has an anticonvulsant effect lasting only about 15 minutes, it should be followed up by the administration of a longer acting agent like phenytoin.

Phenytoin bolus of 15 to 20 mg/kg should be given at a rate not exceeding 0.5 to 1 mg/kg/minute or 30-50 mg/minute (whichever is less). It should be diluted with twice its volume of normal saline. Owing to the likelihood of precipitation, it should not be mixed with a dextrose solution. Heart rate, blood pressure, and electrocardiogram should be monitored carefully during the infusion. The infusion should be temporarily suspended if hypotension or bradycardia develop, and resumed after normalization of these parameters. The 20 mg/kg bolus produces an immediate therapeutic level of 15-20 microgram/ml.[17] Phosphenytoin (being water soluble does not have sodium hydroxide or propylene glycol) can be given at the rate of 150 mg phenytoin equivalent/min.

If seizure activity persists despite administration of the benzodiazepine and phenytoin (a serum level of 25 microgram/ml if available), phenobarbital 5-10 mg/kg should be given. Owing to the cumulative respiratory depressant effect of benzodiazepines and barbiturates, one should be prepared for endotracheal intubation and for placing the patient on a ventilator. In our PICU we use midazolam in the dosage of 0.1 to 0.3 mg/kg followed by continuous infusion of 0.3 to 10 microgram/kg/min.[18,19]

Propofol 3 mg/kg bolus, then 1 to 15 mg/kg/hour infusion can also be used for refractory SE.

If seizure activity persists, pentobarbital coma is recommended 5 to 10 mg/kg of the pentobarbital should be administered every 2-3 hours till a burst suppression pattern is visualized on the electroencephalogram. The coma should be maintained for about 24 hours, following which it should be gradually terminated.[20, 21] Coma may be maintained safely for up to three days with a continuous infusion of 3 mg/kg/hour. The EEG (ideally) should be continuously monitored or should be checked several times each day for burst suppression. Longer periods of pentobarbital coma are associated with hypotension, and pulmonary edema.

Alternative Therapy

As mentioned previously, in case intravenous access is difficult, diazepam 0.4-0.5 mg/kg/dose of the standard parenteral preparation may be given undiluted per rectum.[22] Alternatively, paraldehyde 15 ml/meter square to maximum of 15 ml may be given by the same route. Paraldehyde breaks down upon exposure to light into acetaldehyde and acetic acid. The physician should therefore, ensure that the solution is crystal clear. It should be mixed with an equal amount of mineral oil and administered as a retention enema. Both rectal diazepam and paraldehyde have onset of action within ten minutes. Repeated administration of rectal paraldehyde should generally be avoided owing to the risk of mucosal ulceration. Paraldehyde is a general anesthetic; 70 to 80 percent is metabolized in the liver, and the remainder is excreted unchanged by the lungs. It can only be used in well-ventilated patients with adequate liver function. A 5 percent solution in 5 percent dextrose can also be infused drop by drop, titrating the seizures until they stop. Diazepam can also be used as a continuous infusion if other drugs such as lorazepam or midazolam are not available in the Indian setting.

Treatment of NCSE

The diagnosis of non-convulsive status epilepticus should be confirmed by EEG. Intravenous lorazepam or diazepam should be administered while the EEG is being monitored. This leads to resolution of the status in most instances, following which the appropriate oral anticonvulsant may be started (Sodium valproate in the case of absence status and phenytoin/carbamazepine in case of complex partial status)

Seizures due to drugs, and drug *withdrawl*, should be treated with short term anticonvulsant therapy. PICU patients with central nervous system disease should be maintained on chronic anticonvulsant therapy. Various old and newer antiepileptic drugs (AEDs) for chronic anticonvulsant therapy are discussed in the following section.

The management of epilepsy in the pediatric patient requires careful evaluation, classification, and pharmacologic treatment. Despite best efforts on the part of clinicians, approximately 25 percent of children remain refractory to appropriate medical therapies. The development of an improved classification system and the emergence of several new antiepileptic drugs have enabled some progress in this area, specifically in children with disorders such as Lennox-Gastaut syndrome and infantile spasms, which are notoriously difficult to control.

New Antiepileptic Drugs

For many years, therapy with standard AEDs was the only option for the pharmacologic treatment of children and adults with epilepsy. Although these drugs generally were effective in controlling seizures, their usefulness was hampered by unfavorable adverse effect profiles and unwanted drug interactions. Several new AEDs have been introduced during the 1990s and are presented here in alphabetical order.

Felbamate

In 1993, felbamate was labeled for adjunctive treatment of partial and generalized seizures in children with Lennox-Gastaut syndrome. There were numerous reports of hepatotoxicity and aplastic anemia in adults, but there have been no reports of aplastic anemia in children younger than 13 years. Felbamate is therefore a treatment option in children whose seizures are not controlled with traditional AEDs. It proved to be highly beneficial in a study of children older than 10 years, who had a more than 50 percent reduction in the frequency of seizures while taking felbamate. Major side effects include aplastic anemia (possibly at a rate of one case per 8,000), anorexia, somnolence, nausea and vomiting, and gait abnormalities. An initial adjunctive dosage is 15 to 45 mg per kg per day, but much higher dosages may be needed. The author recommends that this drug be taken only in consultation with a pediatric neurologist.

Gabapentin

Gabapentin is labeled by the FDA for adjunctive treatment of partial and secondarily generalized seizures in adults. It can be titrated quickly and easily, and its adverse effects (e.g., behavioral changes and aggression) are mild. Gabapentin's efficacy in children seems to be dosage-dependent. Initial dosage recommendations are 10 to 20 mg per kg per day, increasing to 30 mg per kg per day. Some children may need dosages as high as 60 to 100 mg per kg per day. One study showed particularly good response in mentally retarded children who had resistant partial epilepsy.

Lamotrigine

Lamotrigine is given to children in dosages ranging from 1 to 15 mg per kg per day. Careful dosing attention is needed because adverse effects are much more common at higher dosages. Serious rashes have been reported in up to 12 percent of patients, often in children who are also taking valproate and whose dosage is titrated rapidly. The rash may progress to Stevens-Johnson syndrome or toxic epidermal necrolysis. Lamotrigine seems to be especially useful in children with Lennox-Gastaut syndrome, generalized epilepsy syndromes and refractory partial epilepsy.

Tiagabine

Tiagabine is labeled for adjunctive treatment of partial seizures. Although higher dosages (up to 56 mg per day) seem to be most effective, dosing starts in children at 0.1 mg per kg per day. As with most newer AEDs, data in children are limited, but this medication seems to be effective in children with partial seizures. Tiagabine selectively inhibits the uptake of g-aminobutyric acid and, as such, might be useful in the treatment of infantile spasms. Further studies are needed. Side effects include headache, dizziness and somnolence. Topiramate may be useful as adjunctive and monotherapy in children with refractory partial seizures. The initial dosage is 1 mg per kg per day, with titration up to 6 mg per kg per day. Major side effects include somnolence, dizziness, psychomotor slowing, paresthesias and confusion. Some adult patient have also developed nephrolithiasis and weight loss

One investigational medication, **vigabatrin**, ha been shown to be quite effective in a number o pediatric epilepsies, especially infantile spasms. I has also been used successfully in children wit Lennox-Gastaut syndrome but may exacerbat myoclonic seizures.

The author concludes that first-line treatment o pediatric epilepsy should still involve the use o conventional AEDs. However, the newer AED offer more options, especially in children wit refractory seizures. The *accompanying tab* summarizes treatment guidelines for ne antiepileptic drugs.

Guidelines for the Use of New Antiepileptic Drugs

Drug	FDA-labeled indication(s)	Pediatric dosage	Adverse effects
Felbamate	Treatment of partial seizures with or without secondary generalization in adults; adjunctive treatment of partial and generalized seizures in children with Lennox-Gastaut syndrome	15 to >75 mg per kg per day	Anorexia, aplastic anemia,* gait abnormalities, hepatotoxicity,* insomnia, nausea, somnolence, vomiting, weight loss
Gabapentin	Adjunctive treatment of partial and secondarily generalized seizures in adults	30 to >90 mg per kg per day	Ataxia, behavioral changes, dizziness, fatigue, nystagmus, somnolence, weight gain
Lamotrigine	Adjunctive treatment of partial seizures in adults; adjunctive treatment of generalized seizures in children with Lennox-Gastaut syndrome	1 to >15 mg per kg per day	Ataxia, diplopia, dizziness, headache, nausea, rash (potentially Stevens-Johnson syndrome),* somnolence, vomiting
Tiagabine	Adjunctive treatment of partial seizures	32 to 56 mg per day	Dizziness, headache, somnolence, twilight state
Topiramate	Adjunctive treatment of partial seizures in adults	3 to >10 mg per kg per day	Abnormal thinking, ataxia, confusion, diplopia, dizziness, fatigue, headache, impaired concentration, nystagmus, paresthesia, psychomotor slowing, somnolence, speech difficulties

FDA = U.S. Food and Drug Administration.—Black box warning.Reprinted with permission from Pellock JM. Managing pediatric epilepsy syndromes with new antiepileptic drugs. Pediatrics 1999;104:1113.*

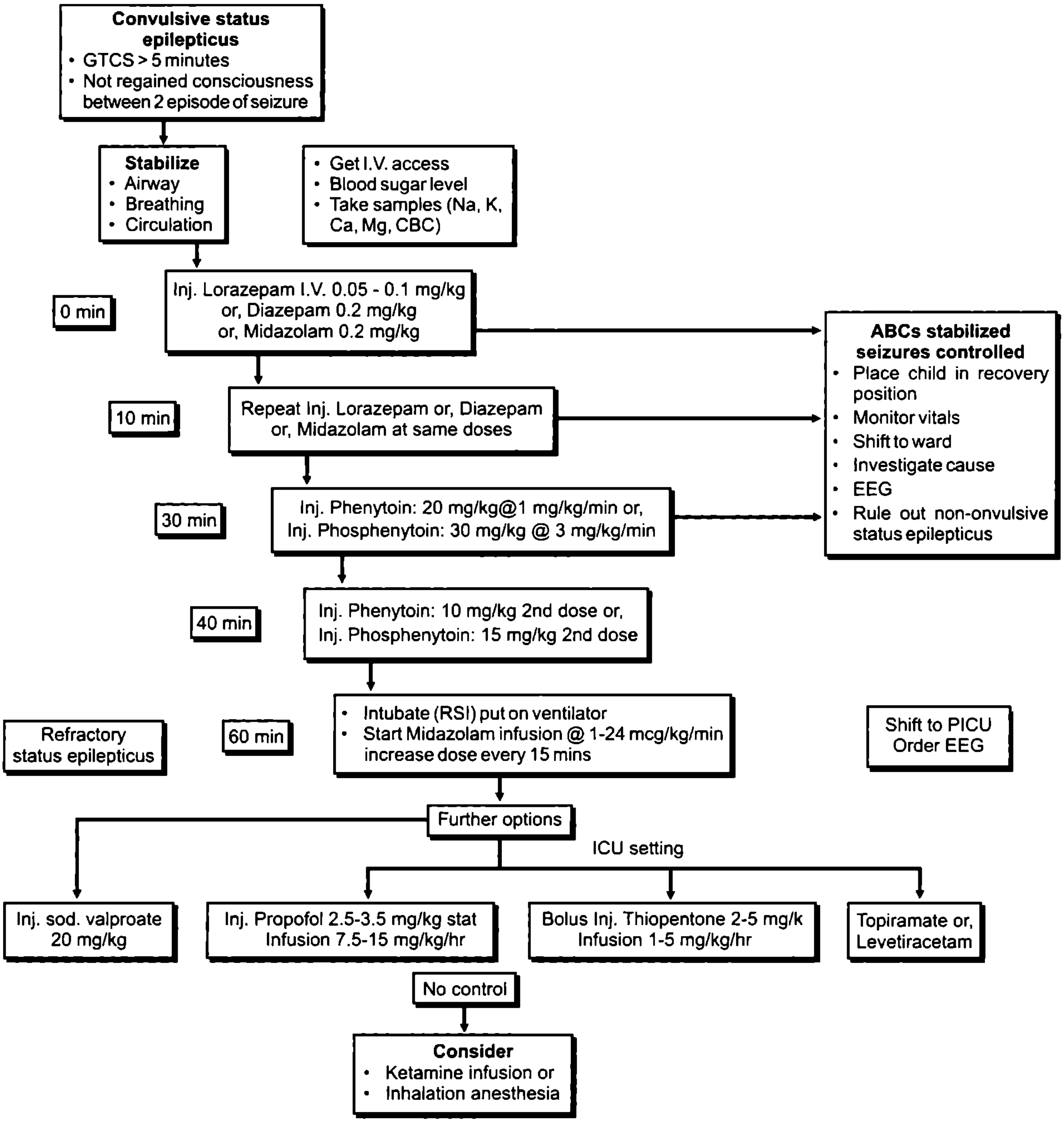
Prognosis and Outcome

Aicardi and Chevrie, in a 1970 study[23] found a 11 percent mortality and 57 percent morbidity from status epilepticus. Rowan and Scott[24] noted that the mean duration of status in patients who did not suffer neurologic sequelae was 1.5 hours, 10 hours in patient who had neurologic sequelae, and 13 hours in patients who died. In another series, Maytal et al[25] reported only two deaths in a series of 102 patients, and 21 of the survivors developing a static encephalopathy. They felt that in the absence of an acute neurologic insult or a progressive neurologic disorder, the morbidity from status is low. In another study by Dunn,[26] the mortality was 8 percent, and morbidity 19 percent. They also recognized that the presence of brain edema on the CT scan is an indicator of poor outcome. The lower mortality and morbidity in recent years may be related to improvements in intensive care facilities for children, as well as the availability of better anticonvulsants. Neither Maytal et al or Dunn however, have published a long term follow-up on those patients. The possibility of the development of less subtle sequelae from SE, e.g. learning difficulties, cannot therefore be commented upon at this time. There is a concern about permanent memory deficits following prolonged complex partial status epilepticus.[27] Age less than three years, and seizures lasting more than 1.5 hours also appear to be poor prognostic factors.

SUMMARY

Status epilepticus is a medical emergency and necessitates prompt attention. Initial assessment should be rapid and includes attention to airway and breathing, history leading up to status, and neurologic examination. A controlled airway must be established immediately and bag mask ventilation instituted with 100 percent oxygen. Venous access is established. Blood is withdrawn for glucose, electrolytes and anticonvulsant concentrations as applicable. Other tests (i.e. toxic screen) are performed as indicated. An intravenous bolus of 1 ml/kg of a 50 percent glucose solution is considered if quick blood glucose is not available. If diazepam is chosen as a first drug, the dose is 0.2 mg/kg, not to exceed 10 mg at a rate of 1 mg/minute. Lorazepam is probably preferable to diazepam because of its longer action (Flow chart 90.1). The usual dose in children twelve years or younger is 0.1 mg/kg; 0.07 mg/kg is used in adolescents. In prehospital situation rectal diazepam (0.4 to 0.5 mg/kg) or nasal midazolam (0.05 to 0.3mg/kg) can be used. Children who are given intravenous diazepam after a prior load of barbiturate may experience respiratory depression. Intravenous phenytoin 15 to 20 mg/kg is injected at a rate not to exceed 0.5 to 1 mg/kg/minute. Newborns and infants generally require 20 mg/kg. The slow rate of administration is used to avoid cardiac dysrhythmias. Sodium, potassium, calcium and magnesium must be normalized.

Flow chart 90.1: Convulsive status epilepticus (SE)


Convulsive status epilepticus
• GTCS > 5 minutes
• Not regained consciousness between 2 episode of seizure
Stabilize
• Airway
• Breathing
• Circulation
• Get I.V. access
• Blood sugar level
• Take samples (Na, K, Ca, Mg, CBC)
0 min
Inj. Lorazepam I.V. 0.05 - 0.1 mg/kg or, Diazepam 0.2 mg/kg or, Midazolam 0.2 mg/kg
ABCs stabilized seizures controlled
• Place child in recovery position
• Monitor vitals
• Shift to ward
• Investigate cause
• EEG
• Rule out non-onvulsive status epilepticus
10 min
Repeat Inj. Lorazepam or, Diazepam or, Midazolam at same doses
30 min
Inj. Phenytoin: 20 mg/kg@1 mg/kg/min or,
Inj. Phosphenytoin: 30 mg/kg @ 3 mg/kg/min
40 min
Inj. Phenytoin: 10 mg/kg 2nd dose or,
Inj. Phosphenytoin: 15 mg/kg 2nd dose
Refractory status epilepticus
60 min
• Intubate (RSI) put on ventilator
• Start Midazolam infusion @ 1-24 mcg/kg/min increase dose every 15 mins
Shift to PICU
Order EEG
Further options
ICU setting
Inj. sod. valproate 20 mg/kg
Inj. Propofol 2.5-3.5 mg/kg stat
Infusion 7.5-15 mg/kg/hr
Bolus Inj. Thiopentone 2-5 mg/k
Infusion 1-5 mg/kg/hr
Topiramate or, Levetiracetam
No control
Consider
• Ketamine infusion or
• Inhalation anesthesia

Midazolam infusion (0.3 to 10 microgram/kg/min) can be used for treatment of status epilepticus. If midazolam is not available diazepam infusion can also be used before considering pentobarbital infusion. When using above drugs, attention to ventilation, hemodynamic status and EEG monitoring in the PICU is essential. In patients with status epilepticus due to encephalitis or hypoxic ischemic injury, measures to control intracranial hypertension also need to be instituted. Mortality in published series is 8 percent with a morbidity of 19 percent.[26]

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CHAPTER

Near-drowning

Bala Ramachandran

Drowning is one of the most tragic conditions seen in Pediatrics. Despite the availability of various new therapeutic modalities, the morbidity and mortality associated with near drowning is still very high. "Within minutes, previously normal children with hopeful futures die or are left severely incapacitated with very little chance of meaningful cognition".[1] The fact that most episodes are preventable only adds to the tragedy.

Definition

Drowning is death from submersion in water within 24 hours of the incident. Death is usually immediate, due to asphyxiation at the time of the event, or occurs within 24 hours. If the victim survives for at least 24 hours, it is called near drowning, regardless of the eventual outcome.[2] Secondary drowning is a term that has been used in the past to refer to the delayed onset of respiratory distress or to a complication of drowning.

Epidemiology

In the United States, there are more than 2000 deaths each year in persons aged below 19 years due to drowning.[2] There is a bimodal distribution, with deaths being higher in all children under 5 years and in males 15-19 years of age. Accidental drowning is the second commonest cause of non-intentional injury in children and the incidence in males is four times that in females. The World Health Organization has reported that drowning is the leading cause of death for males in the age group 5 to 14 years and is the fifth leading cause of death for females in the same age group, worldwide. For both sexes combined, drowning is the fourth leading cause of death, exceeded only by acute lower respiratory infections, malaria and motor vehicle accidents, in the 5 to 14 year age group.[3]

In Bangladesh, drowning has been reported to cause between 10 to 25 percent of childhood deaths.[4]

In one study from India, 19.4 percent of deaths in children between the ages of 1 to 12 years, in a rural area, were due to drowning. Males had more than twice the drowning rate of females.[5] Thus, it is evident that drowning is a serious public health problem around the world. Ironically, many young children drown while under the care of a responsible adult. In addition, it has been reported that 90 percent of drownings occur within 10 meters of safety.[6] Even expert swimmers can drown while swimming underwater, particularly if they have resorted to hyperventilation before swimming in order to increase the duration spent underwater. Other factors that may also play a role include alcohol and drug abuse, especially in the adolescent population. Certain medical conditions, such as seizure disorders and the prolonged QT syndrome, are also associated with an increased risk of drowning. Persons with seizure disorders have been reported to have four times the risk of drowning, when compared with the normal population.[7] The prolonged QT syndrome, which can also be familial (Romano Ward syndrome), should be considered in cases of unexplained near drowning, especially if there is a family history of syncope, palpitations or sudden deaths.[8,9]

Pathophysiology

Prolonged submersion results in global hypoxic injury. The sequence of events after submersion has been studied in both animals and humans. Initially, there is a period of panic and voluntary breath holding, accompanied by violent struggling and automatic swimming movements.[1] As the pCO_2 increases there are involuntary contractions of the diaphragm, while the glottis is kept closed voluntarily. Eventually, there is an involuntary gasp, which may result in aspiration of water into the lungs. 10-20 percent of patients have severe laryngeal spasm, which results in no aspiration—this is known as Dry Drowning. However, most patients swallow large amounts of water and this may be aspirated passively due to vomiting. The victim loses consciousness rapidly due to hypoxia. The first gasp is followed by a stage of secondary apnea. Then there are several involuntary gasps, followed eventually by a respiratory arrest. Cardiac arrhythmias and convulsions may occur before death.

Fluids and Electrolytes

Much has been written about the type of water in which the accident occurs. Fresh water is hypotonic with respect to plasma and may cause hypervolemia and hemodilution, resulting in hypoelectrolytemia and hemolysis. Salt water is hypertonic and draws water into the lungs, resulting in pulmonary edema, hypovolemia, hyperelectrolytemia and hemoconcentration. However, these data are from animal studies in which large volumes of water (22 ml/kg) were instilled into the trachea. Aspiration of more than 11 ml/kg of fluid is required for blood volume to be altered and aspiration of more than 22 ml/kg of fluid is needed before significant electrolyte disturbances occur.[2] Most patients aspirate less than 3 to 4 ml/kg body weight. In clinical practice, the type of water is generally not very important and most victims are functionally hypovolemic because of the generalized capillary leak resulting from hypoxic endothelial damage and the subsequent loss of protein rich fluid into third space. Most patients are also hyper-glycemic due to a stress related secretion of endogenous catecholamines.

Pulmonary Effects

During the submerged phase, Functional Residual Capacity is the only source of gas exchange. Hypoxia and hypercarbia develop rapidly. There is a combined respiratory and metabolic acidosis due to hypercapnia and anaerobic metabolism. Patients without significant aspiration recover quickly if they are resuscitated successfully, before the onset of cardiac arrest or hypoxic brain damage. However, the aspiration of as little as 1-3 ml/kg of fluid results in severe derangement of gas exchange.

Aspirated water affects the pulmonary surfactant mechanisms. Fresh water denatures surfactant whereas salt water dilutes surfactant or washes it out of the alveoli. There is resultant atelectasis, decreased lung compliance and increased intrapulmonary shunting, all of which lead to hypoxia. This hypoxia may persist for many days, even if the patient is otherwise normal.

Injury to the alveolar endothelium results in increased membrane permeability, exudation of protein rich fluid into the alveoli, pulmonary edema, decreased lung compliance and increased airway resistance. There is pulmonary vasoconstriction and pulmonary hypertension. These changes may evolve into the Acute Respiratory Distress syndrome. Some patients may initially respond to therapy but have significant respiratory deterioration later. This is known as Secondary Drowning and is defined as the occurrence of respiratory dysfunction after successful resuscitation.[1] Secondary drowning may occur up to 72 hours after rescue. Late respiratory deterioration can also be due to pneumonia, aspiration of mud, foreign bodies or stomach acid, or ventilator induced lung injury.

Central Nervous System (CNS) Effects

Primary CNS injury occurs at the time of the accident. However, the course of events during and after resuscitation can contribute to secondary injury. These include persistent hypoxia due to pulmonary causes, hypotension due to hypovolemia and cardiac dysfunction.

After restoration of circulation there is a transient period of cerebral vasodilatation, followed by a prolonged period of severely decreased cerebral blood flow, which also contributes to the ongoing neurological injury. There is raised intracranial pressure, cytotoxic cerebral edema, accumulation of cytosolic calcium and the production of oxygen derived free radicals.[2] Cerebral edema usually develops 24 to 72 hours after the initial event.[1]

The raised ICP further potentiates CNS damage. The increased calcium causes cerebral vasospasm, contributing to the cerebral ischemia. Reperfusion of hypoxic tissues results in the formation of oxygen free radicals, such as superoxide and hydroxyl radicals. These cause lipid peroxidation and severely damage cell membranes.

With improved technology and management of the multisystem dysfunction seen after near drowning, the degree of CNS damage is the major determinant of outcome.

Cardiovascular Effects

Near drowning victims can have severe cardiovascular instability. There may be various rhythm disturbances, such as bradycardia progressing to asystole, supra-ventricular tachycardia, and, occasionally, ventricular fibrillation. Most arrhythmias are due to hypoxia rather than electrolytes abnormalities.

The most common cardiovascular abnormality seen after near drowning is cardiogenic shock due to hypoxic damage to the myocardium, compounded by metabolic acidosis. There is poor contractility, intravascular hypovolemia leading to inadequate preload, increased systemic and pulmonary vascular resistance, leading to increased afterload, all of which impair myocardial performance.

Effects on Other Organ Systems

All systems can be affected by the hypoxic ischemic damage. Renal dysfunction may manifest as hemoglobinuria, albuminuria, hematuria, oliguria or anuria due to acute tubular necrosis. There may be rhabdomyolysis, which can contribute to the renal injury.[10] Liver damage can occur, resulting in elevated transaminases, bilirubin and decreased production of coagulation factors. This contributes to the disseminated intravascular coagulation that may be seen. Gastrointestinal injury can cause mucosal soughing. These patients are at high risk for perforation or sepsis due to bacterial translocation.

Hypothermia and the Diving Reflex

Drowning in cold water may confer some protection. Good outcomes have been reported in both adults and children after prolonged submersion in cold water.[11-15]

The body rapidly loses heat and becomes hypothermic in cold water. This process is much faster in children due to their large surface area. Severe hypothermia causes a decrease in energy consumption. There is reduced cerebral blood flow and reduced cerebral oxygen utilization. The pupils dilate and are nonreactive below 30°C. The EEG becomes flat below 20°C. Cardiac dysrhythmias, such as ventricular fibrillation, may occur. Such persons appear dead but it may still be possible to revive them. In order for the protective effect, rapid cooling in icy water (below 5°C) is necessary. Water warmer than this does not confer any protection. It has to be pointed out that intact survival after prolonged submersion in icy water is an exception rather than the rule. The mammalian diving reflex is a protective mechanism seen in certain marine mammals, such as seals, that are able to remain submerged for long periods without harm. There is a redistribution of blood flow away from tissues more resistant to hypoxia while submerged. The exact role of the diving reflex in protecting children during cold-water submersion is still unclear.

ASSESSMENT AND MANAGEMENT

Management at the Scene

The complete extent of CNS injury cannot be determined accurately immediately after the accident. Rescuers and bystanders will be emotionally excited and estimates of submersion time will not be reliable. Therefore, all victims should receive aggressive basic and advanced life support, both at the scene and in the emergency room.[2] If the rescuer knows basic life support, mouth-to-mouth respiration can be performed in the water itself, as soon as the victim has been pulled to the surface. However, chest compressions are ineffective in water and time should not be wasted in attempting these. Once the victim has been brought to land, standard Basic Life Support (BLS) guidelines apply. If there are persons who can provide BLS, they should do so, while simultaneously arranging for the victim to be transported to the nearest medical facility without further delay. The use of the Heimlich maneuver has been recommended in the past to remove water from the airways. However, most victims aspirate only a small amount of water. In addition, most victims swallow large amounts of water-performing sub-diaphragmatic thrusts can increase the likelihood of regurgitation and aspiration of swallowed water. The Heimlich maneuver should not be performed routinely and is indicated only if obstruction of the air passages by a foreign body or debris is suspected.[16] It must also be kept in mind that the victim may have suffered other injuries, such as injury to the cervical spine, head injury or trauma to other systems, depending on the mechanism of injury. In one study of over 2,200 submersion victims, 0.5 percent had cervical spine injury and all of these were associated with high impact submersion, such as fall from a height or a diving accident.[17]

Management in the Emergency Room

The initial principles of resuscitation are the same as for any other patient, namely, Airway, Breathing and Circulation. If the patient is breathing spontaneously, supplemental oxygen is all that may be needed. Otherwise, artificial respiration should be started after ensuring that the airway is patent. Once the Airway and Breathing have been attended to, the circulatory status should be assessed, including the presence of a pulse, heart rate and perfusion. Chest compressions are started if clinically indicated. Basic monitoring in the Emergency Room should include pulse oximetry and cardiac monitoring, since dysrhythmias can occur in the near drowning victim. Initial laboratory tests should be ordered, including electrolytes, glucose, hemoglobin and an arterial blood gas to assess the degree of hypoxia and acidosis. In selected cases, renal and liver function tests should also be obtained. The degree of derangement in the liver function tests is indirect evidence of the amount of hypoxic multisystem damage. A chest X-ray should also be obtained, depending on the clinical examination. The initial chest X-ray may show evidence of pulmonary edema, aspiration, pneumothorax, or may be entirely normal (Fig. 91.1).

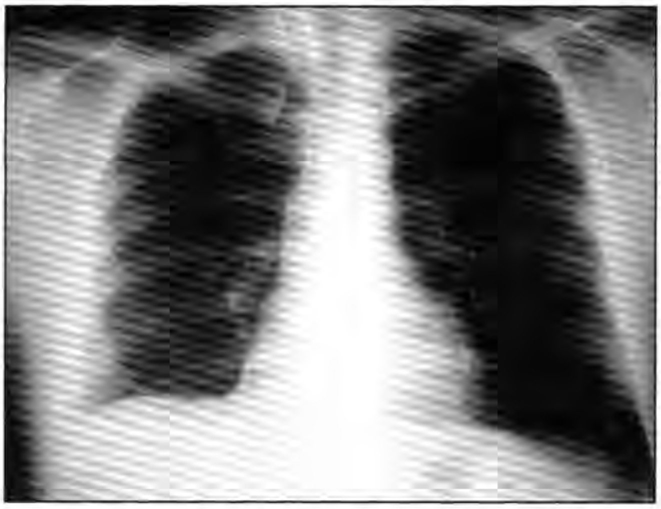

Fig. 91.1: Pulmonary edema in near drowning
(Reproduced from Gluecker T, Capasso P, et al. Clinical and radiological features of pulmonary edema. Radiographics 1999;19:1507-31).

In addition to the routine vital signs, the patient's Glasgow Coma Score should be obtained in the emergency room, since this has prognostic value. The core body temperature should also be measured. Hypothermia may be missed unless the rectal temperature is measured with a special thermometer capable of reading low temperatures. At temperatures below 30°C the myocardium is resistant to defibrillation and drugs. Therefore, CPR should be continued while the patient is being rewarmed. Most patients will be functionally hypovolemic and a fluid bolus of an isotonic crystalloid, 20 ml/kg, should be given intravenously. Additional fluid boluses are administered as clinically indicated. Most patients will also be hyperglycemic and glucose containing fluids should not be administered unless there is hypoglycemia. An elevated initial blood glucose level has been associated with higher mortality.[18] A nasal or orogastric tube should be inserted in the emergency room and the stomach aspirated to remove any swallowed water that is still present. An indwelling urinary catheter should also be inserted in all seriously ill patients. Patients who have aspirated even small quantities of fluid will be hypoxic. If the hypoxia does not respond to supplemental oxygen (pulse oximetry less than 90%on more than 50% oxygen), then positive pressure should be administered. Some patients can be managed with Continuous Positive Airway Pressure (CPAP) alone. This can be administered through CPAP nasal prongs in infants or via a tight fitting mask in older co-operative patients.[19]

However, many physicians prefer to perform tracheal intubation. Intubation has certain advantages, such as providing a secure airway, allowing good pulmonary hygiene and provides samples of aspirate for culture. There should be a low threshold for intubation. Criteria include the loss of protective airway reflexes, deteriorating neurological exam, severe respiratory distress or hypoxia, respiratory acidosis, cardiac arrest and severe hypothermia.[1] All patients with a history of near drowning should be observed in the emergency room for at least 6 hours. Those who have any respiratory symptoms, decreased oxygen saturation by pulse oximetry or altered sensorium should be admitted to the hospital. Those who are intubated or have a significant oxygen requirement should be transferred to the pediatric intensive care unit (PICU). The remainder can be treated on an outpatient basis, provided good follow-up is possible. If follow-up cannot be assured or if the patient lives far away, it is better to admit them to hospital since even healthy looking patients can deteriorate later.

Management in the PICU

Near drowning causes global hypoxic-ischemic injury and affects every organ system. The aim of intensive care is to provide supportive care while allowing the damaged systems to recover and to prevent further damage, both from the initial insult and from the therapy. This will maximize the chances of meaningful recovery.

Monitoring

In addition to routine cardio-respiratory monitoring, non-invasive blood pressure and pulse oximetry, most patients will benefit from invasive monitoring of the arterial blood pressure and central venous pressure. An arterial line also allows frequent sampling of blood for blood gases and other tests. Central Venous Pressure monitoring is invaluable in those with hemodynamic dysfunction and shock since it allows measurement of the filling pressures on the right side of the heart. Many centers, especially in the United States, also insert a thermodilution Pulmonary Artery catheter in patients with extreme hemodynamic instability or intractable hypoxia. This is useful to measure cardiac output, pulmonary arterial and wedge pressures, and to calculate the vascular resistances, measures of oxygen delivery/consumption and indices of ventricular function. It also allows measurement of mixed venous oxygen saturation (SvO_2). However, it is technically more difficult to insert in children and its role has been questioned by many. The use of Pulmonary Artery catheters is declining and is being substituted by repeated echocardiograms.[20] End tidal CO_2 monitoring is useful in patients who are intubated. Frequent assessment of the neurological status, including the Glasgow Coma Score and the pupils, is mandatory.

Monitoring the urine output with an indwelling catheter is an excellent indicator of the efficacy of resuscitation.

HYPOTHERMIA

Hypothermia is a major problem, especially in children. Steps to prevent further heat loss, such as removing wet clothes, and to rewarm the patient should be instituted in the Emergency Room itself and continued in the intensive care unit. Victims with a core temperature > 30°C should be rewarmed by active external measures. These include blankets, overhead radiant warmers, hot water bottles and forced air convective warmers. The latter are especially efficient means of warming.[21] However, active internal rewarming is required for patients whose core temperature is below 30°C. External measures alone in such patients will create a vasodilated bed whose metabolic needs cannot be met by a cold, poorly functioning heart.[1] There is also the risk of localized burns at the sites of external warming, since the poor circulation cannot dissipate the heat emitted by external warming sources effectively. Internal rewarming can be achieved by using warm intravenous fluids, warmed humidified gases through the ventilator, gastric or rectal lavage with warmed saline and peritoneal lavage. Many centers have also successfully used extracorporeal circuits (Extra Corporeal Membrane Oxygenation (ECMO)/cardiac bypass) to rewarm severely hypothermic patients.[22,23] The profoundly hypothermic victim may have dilated, unresponsive pupils, have various cardiac arrhythmias, including ventricular fibrillation or severe bradycardia. The hypothermic heart is resistant to electrical defibrillation and to cardiac drugs. Due to slow metabolism, resuscitation drugs such as epinephrine and lidocaine may accumulate to toxic levels.[1] Therefore, it is recommended that severely hypothermic patients receive only one dose and further doses be given only after the patient has been warmed to more than 30°C. Defibrillation attempts should also not be performed repeatedly. Instead, cardiopulmonary resuscitation (CPR) should be continued until the patient has been sufficiently warmed before additional shocks are administered. These patients may actually appear to be dead. However, there have been many reports of successful resuscitation and therefore efforts to revive the patient should continue aggressively. No one should be declared dead until the core temperature is more than 32°C.[14,15]

RESPIRATORY MANAGEMENT

The respiratory management of the near drowning victim is often a challenge. Aspiration induced alterations in surfactant mechanisms result in profound hypoxia. Generalized capillary leak due to hypoxic damage leads to non-cardiogenic pulmonary edema, which may progress to the Acute Respiratory Distress syndrome. All patients should be given supplemental oxygen. Some may require positive pressure, as indicated earlier. The use of Positive End Expiratory Pressure is extremely effective in treating hypoxia. PEEP increases the Functional Residual Capacity above Closing Capacity. It improves lung compliance, decreases pulmonary edema, decreases V/Q mismatch and intrapulmonary shunting. Most centers now routinely use PEEP aggressively, up to 20 cm H_2O. Generally, it is started at about 5 cm H_2O and increased in increments of 2-3 cm H_2O until oxygenation improves adequately ($PaO_2/FiO_2 > 300$). The aim is to achieve a saturation of greater than 90 percent on less than 90 percent oxygen, to avoid oxygen toxicity. Once this is achieved, this level of PEEP is maintained for 3-4 days, during which time there is regeneration of pulmonary surfactant and a decrease in the capillary leak. PEEP is weaned gradually, in a stepwise manner. If PEEP levels are greater than 10-12 cm H_2O, most centers paralyze the patient to minimize the risk of barotrauma. In this situation, the patient can have seizures that are not clinically apparent. Though most patients will tolerate PEEP well, it does reduce the cardiac output and therefore the intravascular volume must be maintained at an adequate level. In addition, it is customary to use lower levels of PEEP when managing patients with increased intracranial pressure. However, oxygenation takes priority and as much PEEP as is needed to maintain adequate oxygenation must be used, even if the patient has increased ICP. The ventilatory approach to managing these victims is no different from that of any other patient with ARDS. Generally, a pressure-controlled mode is preferred to minimize the peak pressure. Tidal volume is limited to 6 to 8 ml/kg. The mean airway pressure is increased by prolonging the inspiratory time. An extreme form of this is the use of Pressure Controlled Inverse Ratio Ventilation (PC-IRV), in which the I:E ratio is prolonged to 2:1 or even 3:1. One must check for the presence of significant auto-PEEP, which can result in decreased cardiac output. Permissive hypercapnia, wherein CO_2 levels much higher than normal are accepted as long as the pH is acceptable, may not be suitable in all cases since it can predispose to higher intracranial pressures in a patient who already has hypoxic ischemic encephalo-pathy. Several alternative ventilatory strategies have been used, such as prone positioning, pulmonary surfactant replacement, inhaled nitric oxide therapy, partial liquid ventilation and high frequency oscillatory ventilation.[24,25] Of these, High Frequency Oscillatory Ventilation (HFOV) is extremely useful (See Chapter on High Frequency Ventilation). It is a mode of ventilation in which high mean airway pressures (up to 40 cm H_2O) are used at extremely high rates (up to 15 Hz or 900 breaths/minute) and short inspiratory times. It achieves adequate alveolar recruitment and improves oxygenation while minimizing baro and volutrauma. This mode has been shown to be safe and effective in patients with acute respiratory failure that does not respond to conventional mechanical ventilation.[26] When HFOV is available, it is rarely necessary to resort to PC-IRV. Although there have been reports of patients treated successfully with the other techniques, they have not been conclusively proven to be effective and remain investigational at this time. Extracorporeal life support has also been used in managing patients with near drowning with refractory hypoxia. However, there are no controlled studies comparing the use of ECMO in this situation with conventional therapy and the decision to use modalities like ECMO must be made on an individual basis.

Role of Diuretics and Corticosteroids

There is no role for using diuretics in the management of non-cardiogenic pulmonary edema. Since many patients will already be functionally hypovolemic, diuretics may actually exacerbate the problem. Steroids have been advocated in the past for near drowning. However, there is no good evidence to suggest that the routine use of corticosteroids alters the outcome of near drowning and their use is discouraged at this time.[27,28]

Infection Control

Various infections have been reported in victims of near drowning. These range from common bacteria such as *Streptococcus pneumoniae,* to more uncommon ones, including Aeromonas species, Vibrio, Pseudomonas Pseudomallei, *Francisella Philomiragia, Pseudalle-scheria Boydii, Neisseria Mucosus, Aspergillus species and Monosporium Apiospermum.*[29-39] The infections can be pneumonia, empyema, sepsis, brain abscess or disseminated infections. However, administering antibiotics prophylactically has not been shown to prevent the development of pneumonia and may select out resistant organisms. In one study, pneumonia developed in 64 percent of patients treated with prophylactic antibiotics and the majority of organisms isolated were actually resistant to those antibiotics.[40] Therefore, a reasonable approach would be to obtain endotracheal cultures in all ventilated patients on admission and then start broad-spectrum antibiotics empirically in those who were submerged in grossly contaminated water. Other patients should be closely observed for signs of infection, such as fever, leukocytosis, pulmonary infiltrates. Antibiotic therapy is started based on the predominant organisms found on Gram stain of the tracheal aspirate or based on the predominant bacterial sensitivities in the hospital, pending the results of culture and sensitivity.

Cardiovascular Management

There is often significant cardiac dysfunction after near drowning, in the form of poor cardiac output and perfusion, because of hypoxic myocardial damage. Most victims resuscitated after cardiac arrest show a low cardiac index and high systemic vascular resistance. The cardiac enzymes may be elevated but are not routinely measured. The ECG may show ST segment changes. Treatment consists of maintaining an adequate preload by optimizing the intravascular volume and then the judicious use of inotropes, if required. The goal should be adequate end organ perfusion and oxygen delivery.

Neurological Management

With improvements in the quality of critical care, the determining factor in outcome is the level of neurological damage. Various neuroprotective strategies, including hyperventilation, hypothermia, intracranial pressure monitoring, steroids, mannitol, barbiturates and neuro-muscular paralysis have been used in an attempt to minimize cerebral edema and intracranial pressure. However, none has been shown to improve the neurological outcome and several have significant side effects. Accordingly, most centers have given up these therapies in the management of victims of near drowning.

Currently, therapy should be aimed at restoring oxygen supply to the brain as quickly as possible and minimizing secondary damage. This includes maintaining normal temperature, normoglycemia and control of seizure activity. Therapies to treat raised intracranial pressure include elevating the head of the bed, sedation, avoiding noxious stimuli and avoiding fluid overload. Neuromuscular blockers are used only if required to improve oxygenation in severe hypoxia.

Outcome

Of the various causes of hypoxic-ischemic injury, near drowning has been reported to have a higher mortality, longer duration of unconsciousness and poorer cognitive outcome.[41] Among those patients who survive to reach a PICU, 50 to 80 percent have intact neurological survival, 10 percent have neurological impairment and 25 to 30 percent die. Predicting the outcome of near drowning is important since this information is useful when counseling the families of victims and helps to decide when to withdraw or restrict life support measures. Many studies have attempted to use various criteria to determine the outcome. However, none are infallible and should be used as an adjunct to the treating physician's clinical experience.

Submersion times greater than 10 minutes in non-icy water and duration of CPR more than 25 minutes are highly predictive of death or severe neurological impairment. A normal sinus rhythm, reactive pupils and neurological responsiveness at the scene predicted a good outcome.[42] Good outcomes are more likely with submersion times less than 5 minutes and duration of CPR less than 10 minutes. The need for ongoing CPR in the ER has also been linked to a dismal prognosis. The Glasgow Coma Score is easily reproducible and has been used to predict the outcome. A low score (less than 5) is predicted a group of high-risk patients, with a 80 percent chance of mortality or severe neurological damage, whereas a high score (= 6) defined a low risk group of patients with no deaths or severe neurological sequelae.[43] In another report, no patient who arrived to the emergency room (ER) comatose and asystolic survived neurologically intact. All patients with a detectable pulse and blood pressure on arrival to the ER, regardless of their neurological state, recovered to the presubmersion state.[44] All children, who had spontaneous purposeful movements and normal brainstem function 24 hours after near drowning, had a good outcome, whereas those without spontaneous purposeful movements at 24 hours either died or had severe neurological deficits.[45] The CT scan has also been reported to be useful in determining prognosis. Though a normal CT scan of the brain does not predict a good outcome, an abnormal scan during the first 36 hours following a submersion incident has been associated with a dismal prognosis.[46] In an attempt to see which patients can be discharged home early from the ER in uncomplicated near drowning, one study reported that children, who present to the ER with a Glasgow Coma Score = 13, have a normal pulmonary exam and respiratory effort and oxygen saturation on room air of 95 percent at 4 to 6 hours after presentation can be safely discharged home.[47]

PROGNOSIS

Survivors of near drowning can have a wide range of outcomes, from normalcy to a persistent vegetative state. There may be diminished verbal skills and poor cognition. Patients can have mild incoordination to gross motor deficits. There may be musculoskeletal problems, including contractures, scoliosis, hip dislocation and spasticity. It has also been reported that even asymptomatic survivors have pulmonary dysfunction in the form of peripheral airway disease and bronchial hyperactivity detected on pulmonary function testing.[48] These children may be at an increased risk of developing chronic lung disease.

CONCLUSION

With improved technology and newer techniques of ventilation, the outcome is dependent on the degree of neurological damage. Near drowning is an eminently preventable condition and efforts should be made to prevent these incidents, including education of parents and the public. Increased awareness of Basic Life Support techniques among the public will also benefit victims.

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CHAPTER

92

Brain Death in Children

Praveen Khilnani, Pushpendra N Renjen

Most states in the United States now have laws on Brain Death, and the American Medical Association, the American Bar Association, the National Conference of Commissioners on Uniform State Laws, the President's Commission for the study of ethical problems in medical and Biomedical Behavioral Research and this task force have all endorsed the following regarding the *determination of death;* an individual who has sustained either

i. *Irreversible cessation of circulatory and respiratory function* or
ii. *Irreversible cessation of all functions of the entire brain, including the brain stem, is dead.*

A determination of death has to be made in accordance with accepted medical standards. The government of India passed the Transplantation of Human Organs Bill, 1994, for the regulation for removal, storage and transplantation of human organs for therapeutic purposes and for the prevention of commercial dealings in human organs. "Brainstem Death" means the stage at which all functions of the brain have permanently and irreversibly seized. Death is a natural biological process. What death is and when it has occurred and how it should be determined has played on the minds of physicians, clergy, ethicists and lawyers over the past three decades. Death is a universal phenomenon signifying the end of human existence. In the United States and Europe, brain death is equated legally and medically with the death of a person, however, it is not so in Denmark and Japan.

Criterion of Death

Death has been defined as:

- Permanent cessation of the organism as a whole not of the whole organism, it does not require cessation of function of every neuron.[1]
- Death of the organism as a whole refers to that set of vital functions of integration, control and behaviors that are greater than the some of the parts of the organisms, and those operate in response to demands from the organism internal and external milieu to support its life and to maintain death.
- All three categories of critical functions must be permanently lost.
  1. Vital functions of spontaneous breathing, and autonomic control of circulation.
  2. Integrating physiological response to baro receptors, chemo receptors and neuro endocrine feed back loops.
  3. Consciousness required for the organism to respond to need for hydration, nutrition, protection, etc.

The first set of brain death criteria was introduced to the medical community in 1968, i.e. the Harvard criteria (Table 92.1).[2]

Impact of the transplant era: In the past few decades transplant surgery has evolved rapidly leading to concerns regarding the exact procedure of organ donation and the clinical criteria applied to donor for organ procurement.

Table 92.1: Harvard criteria for brain death (1968)

- Unresponsiveness, temperature >32.2 degrees celcius
- Absence of depressant drugs
- No spontaneous movements
- Apnea-off respirator for 3 minutes on room air
- No reflexes including:
  - Decerebrate or decorticate posturing
  - Pupils-fixed and dilated
  - Swallowing, vocalization
  - Corneal and pharyngeal reflexes
  - Stretch and deep tendon reflexes
- Isoelectric electroencephalogram

All of the above should be repeated after 24 hours

These criteria are still followed to date with some minor modifications.

Pittsburgh Protocol[3]

University of Pittsburgh is a major organ transplant center in the world. Following is a protocol followed at this institution.

"Procurement of organs can not begin until patient meets the cardiopulmonary criteria of death: The irreversible cessation of cardiopulmonary function.

Pulse pressure must be zero.

Patient should be apneic, unresponsive and must meet electrocardiographic criteria of two minutes of ventricular fibrillation, or two minutes of asystole or two minutes of EMD (electromachanical dissociation).

The donor has volunteered to donate organs only after having exercised his/her right to refuse any further life prolonging treatment aimed at resuscitation from cardiopulmonary arrest".

Bernat[1] has argued that at the time the organs are being procured in the Pittsburgh protocol, death has not yet occurred. It certifies the physician to kill dying patient to procure their organs; that is for the benefit of others.The controversy continues over this issue.

Over the years, different criteria evolved and in 1987 the American Academy of Pediatric (AAP) task force on brain death[4] developed guidelines for the determination of brain death in children. *Clinical death is total cessation of respiration and circulation.* Near drowning victims who have been submerged in ice or water for nearly 45 minutes have been successfully resuscitated, though declared clinically dead. *Brain death includes absence of both cerebral and brainstem functions.*

Current criteria of brain death avoid application to "young children". The report of the presidential commission outlines the criteria valid in children older than 5 years. It is generally assumed that the childs brain is more resistant to insults leading to death, although this issue is controversial and lacks convincing clinical documentation. The brain death criterion outlined is useful for determining brain-death in infants and children. In newborns (more than 38 weeks gestation), the criteria are useful 7 days after the neurological insult. The newborn is difficult to evaluate clinically after perinatal insults. This relates to many factors including difficulty of clinical assessment, determination of approximate cause of coma and the certainty of the validity of laboratory tests.[5-8]

These problems are accentuated in a premature infant. However, after an interval, currently suggested as the first seven days after the insult in a term newborn, the extent and reversibility of neurological injury can be determined by the results of physical examination and laboratory tests.

There are no unique legal issues in determining brain death in children as compared with adults.[9] The unique issues are all medical ones and related directly to the one more difficult task of confirming brain death in young children.

HISTORY

a. Determine the etiology of coma and eliminate all reversible and remedial causes
b. Exclude drug overdoses.
c. Absence of metabolic imbalance.
d. Presence of neuro-muscular blockade must be excluded.

Physical Examination

a. Normothermia
b. Normal Blood Pressure
c. Neurological examination includes absence of corneal reflexes, conjunctival reflexes, oculo-vestibular reflexes, oculo-cephalic reflexes, and other reflexes like gag, cough, sucking and rooting. Pupil may be fully dilated or in mid-position throughout the period of observation.
d. Physical finding should remain constant throughout the period of observation
e. Presence of apnea.

Observation Period According to Age

a. Seven days to 2 months, 2 examinations and EEG's–48 hours apart.
b. Two months–1 year; two examinations and EEG's 24 hours apart and/or one examination after an initial flat EEG with absence of cerebral blood flow.
c. More than a year; two examinations 12–24 hours apart; ancillary studies like EEG and radioisotope angiography are optional.

Corroborative Studies

a. EEG
b. Cerebral angiogram : In barbiturate coma
c. Radionuclide flow studies : Dynamic Tc Scan static Tc scan
d. Cerebral blood flow : Doppler ultrasound
e. Multimodality evoked potentials : Brainstem auditory, somatosensory, visual
f. Xenon CT

Apnea Test

1. Adjusts the ventilator rate until $PaCO_2$ or Pet CO_2 is 45 mmHg (initial ABG)
2. Preoxygenate with 100 percent oxygen for 5 minutes before testing
3. Disconnect ventilatory support for 5 minutes
4. Deliver O_2 at 6 L/min. via ET (endotracheal tube)
5. ABG and pH obtained at the end of the test
6. $PaCO_2$ must reach 60 mm Hg to confirm apnea

Certification of death occurs at the time of brain death. Documentation of brain death is essential and must be duly signed by an attending Neurologist or Neuro-Surgeon. Difficult cases should be referred to the hospital ethics committee, which will make recommendations after due discussions and deliberation. The physician must always have good rapport with the family members and must be compassionate and empathetic. It is important to achieve an early confirmation of brain death status, not only for possible organ transplantation, but also to avoid wasting economic, social and family resources.

CONCLUSION

Determination and documentation of brain death after the observation period, according to age, is important difference in brain death determination in children as compared to adults. A patient and calm discussion by the PICU (Pediatric intensive care unit) team (pediatric intensivist, neurologist and other team members) with the family explaining the meaning of brain death in practical terms will help the family in making up their mind about organ donation. Prolonging the agony and anxiety of the family members can be minimized and a sympathetic and compassionate approach will help the family to cope with the bereavement of their lost one.

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CHAPTER

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Care of Terminally Ill Children

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INTRODUCTION

Admission of a critically ill child in the PICU is a stress full experience both for the families as well as for the children. There is always an uncertainty regarding the outcome and fear of death is always there in the minds of parents while the child is mainly concerned about the pain related to disease or medical intervention as well as anxiety related to separation from the parent.

Another major issue related to a child's illness is an uncertain outcome even if the primary illness is not an acute emergency. These illnesses include malignancy, HIV disease, chronic debilitating illness, congenital metabolic disorder,or irreversible neurologic illness such as spinal muscular atrophy.

In this chapter, three main issues related to care of a terminally ill child will be addressed.

a. Issues related to a critically ill child dying in PICU and end of life care.
b. Issues related to end stage palliative care (pain, nutrition and comfort care) in a child who has irreversible medical illness likely to lead to death in a relatively finite period.
c. Bereavement and grief.

Stress is a common phenomenon in PICUs, and its important for all concerned with the management of a seriously ill child to understand various sources of stress as stress management is an important issue central to effective management of a seriously ill, and or dying child due to terminal illness, apart from the appropriate medical management.

Common sources of stress for parents of a hospitalized child.[1]

There are several studies that have been done to identify the sources of stress in parents whose children were admitted to pediatric intensive care units. All these studies have found that: Parents experiencing unexpected admission of their child had higher stress scores on all dimensions than planned admission parent. Parents' overall stress levels are highest early on in the experience of hospitalisation and diminish over time (except where things go wrong).

Factors concerning the child (diagnosis, prognosis, experience of pain) and the parents' relationship with their child were major sources of stress and were more important to parents than factors affecting their own comfort, self-care or spiritual needs. Following factors play an important role as contributing to the ongoing stress for the parents of a sick child admitted to the PICU.

1. **Being in a strange environment**
   Problems of being in a strange environment include unfamiliarity with the hospital setting, where it is difficult to know the way around, who does what, where and when to ask for information, how and when things happen, what to expect or what is expected of oneself. Another problem is parent's isolation from usual resources, social networks and one's own usual social roles.
2. **Losing the parental role**
   Child's physical, psychological, social and spiritual needs are met primarily by the family. Illness affects the nature of some or all of these needs and also the ability of the family to meet them. Hospitalization of a child forces changes

in the parents' view of themselves as protectors and nurturers. They may have to relinquish much of their parenting role to the nurses.

3. **Witnessing death of another child**[2]
   In a pediatric intensive care unit, families often form their own support network and become important parts of each other's "family" while their children are ill. The death of someone else's child in the unit will intensify fears of death and feelings of uncertainty about one's own child. This may also cast doubts on the belief that one's own child is receiving the best care possible.
4. **Waiting**[3]
   Waiting has been identified as one of the most stressful parts of the experience for parents of hospitalised children. Most of the time parents are unable to leave an area for fear of missing an important report. This denies them the mobility that is often used to deal with stress and can lead to feelings of powerlessness. Families who wait often feel neglected and forgotten. All of these characteristics may affect the parent's ability to cope with the stress of waiting.
   Often when the outcome is unpredictable the waiting can result in fear, fatigue, anxiety, lack of ability to concentrate, restlessness, inability to eat or drink, anger and frustration. Stressful periods of waiting occur at various different stages in the child's care, these include waiting for admission, for surgery and for discharge, all of these procedures may be unexpectedly brought forward or postponed for a variety of reasons. Parents also have to wait for the results of diagnostic tests and finally during surgery and medical treatment.
5. **Costs of participation**[4]
   Cost may spread over different dimensions including economic, social and personal.
   a. **Economic**- This may include all the expenses involved in the treatment (costs of traveling to hospital, buying meals, medicines, telephones, paying for alternative care for siblings) and loss of income (especially for those who are self-employed).
   b. **Social**- This dimension may include restricted social life and minimal contact with friends or neighbors who may be co-opted in to help.
   c. **Personal** – This may include participation in unpleasant experiences (such as accompanying a child to the anesthetic room, staying with them during a painful procedure or refusing to let them have a drink) has been identified as difficult because it challenges parents' ideas of themselves and their usual roles in providing for or protecting their children.

For all parents of children with serious illness, one of the most important sources of stress will be anxiety about the child itself and his/her condition.

A Child's Reaction to Illness and Hospitalization

Different-age children, depending on their developmental level, have different key concerns or tasks that influence how they perceive all events. Thus, their understanding of illness and hospitalization also differs, depending on their developmental level which is explained in more detail below:

1. **Age group 3 years and under**: Children beow 3 years of age are establishing primary attachments. They are learning to regulate attention and other body functions. While they have access to opportunities for exploration and learning, their caregivers protect them from pain and overwhelming stimuli. Children in this age range have little concept of illness. They view it as an external agent that causes discomfort and pain. They depend almost totally on their external caregivers to relieve them of what bothers them.
2. **Age group 3 to 7 years:** Children in the range of 3 to 7 years of age are typically concerned with abandonment, punishment and bodily harm. They have begun separating and individuating from their caregivers on whom they still remain largely dependent. These children are better able to understand illness as something going on inside themselves, yet often they have unique ideas to explain why they are sick, including the concrete interpretation that the illness is a punishment for real or perceived indiscretions by the child.
3. **Age group 7 to 13 years:** Children between the ages of 7 and 13 years are working to master fears of loss of control and fears of death. These children have a greater understanding of illness and themselves, but they still believe that they have done something wrong or that they acquired the illness through contagion. Children at this age can be told more about their illnesses and can be more actively involved in their treatments.

4. **Age group 13 to 18 years:** Teenagers between 13 and 18 years are primarily concerned with their physical appearance, self-image, real or potential loss of peers, and fears of dependency. Adolescents understand their illnesses in ways approaching those of mature adults. They can test hypotheses logically and entertain numerous causes for their condition. They depend less on their caregivers, are more able to care for themselves, and generally prefer the company of their peers. Under stress, however, they still tend to consider illness to be a punishment for some indiscretion only known to them.

Stress in PICU Team Members

Various factors that are a common occurrence in the PICU lead to stress among PICU team members: Exhausting physical demands of caring for sick children; conflicts between the team members and the child's family; moral dilemmas due to available technological resources to prolong life; making uncomfortable requests like obtaining consent for a postmortem; breaking bad news to the family; family is perceived as difficult; conflicts within the team; and finally, anger at perceived inadequacies.

ISSUES RELATED TO A CRITICALLY ILL CHILD DYING (OR LIKELY TO DIE) IN PICU AND END OF LIFE CARE

In the following section the discussion pertains to various issues related to care of a terminally ill child (including communication with the families of a critically ill child admitted to the PICU), who is at risk of dying, or is refractory to all treatment modalities with imminent mortality.

In general nurses spend more time with patients and families facing the end of life than any other health professionals. In western PICUs, in particular, nurses are intimately involved in all aspects of end-of-life care and they address the myriad of needs facing individuals at this time of life. Expert nursing care has the potential to greatly reduce the burden and distress of those facing life's end and the ability to offer support for the many physical, psychological, social, and spiritual needs of patients and their families. Nurses, individually and collectively, have over the past decades demonstrated commitment to end-of-life care.

In our Indian health care setup, though we do not practice it routinely, it is a good idea to assign and identify a primary nurse for every patient, and as much as feasible, for that nurse to be present during rounds and physician family communication meetings to discuss diagnosis, prognosis, clinical condition, any changes in treatment, response to treatment, anticipated surgery or change in therapy, any new consultations.

End of Life Care Definitions[5]

Certain terminology described below must be clearly understood by all healthcare professionals as it is commonly used in patients facing end of life issues.

Full resuscitation(CPR): Aggressive ICU management up to and including resuscitative attempts.

Withholding of resuscitation (DNR): Aggressive ICU management up to, but not including, attempts at CPR.

Withholding of life support: The considered decision not to institute a medically appropriate and potentially beneficial therapy, with the understanding that the patient will probably die without the therapy in question.

Withdrawal of life support: The cessation and removal of an ongoing medical therapy with the explicit intent not to substitute an equivalent alternative treatment. It is fully anticipated that the patient will die following the change in therapy.

Physician assisted suicide: A medical doctor provides patients with means to kill themselves.

Euthanasia: The intentional killing of a patient by the direct intervention of a doctor, ostensibly for the good of the patient or others.

Brain death: Irreversible cessation of all functions of the brain including the brainstem. In the US brain death is death. This category does not include patients who maintain brainstem function, such as patients with persistent vegetative state.

In the United states, under the Child Abuse Prevention and Treatment and Adoption Reform Act (1985), withdrawal is permitted when treatment: merely prolongs dying, or is "not effective in ameliorating or correcting all the infant's life-threatening conditions" or, is otherwise futile in terms of survival.

Medical Futility

When there is an agreed upon *"goal of treatment"*(such as intact survival), with a *"means"* identified for achieving that goal (for example ICU admission, and treatment with therapy such as mechanical ventilation and other modalities of technology intensive medical care) as well as a virtual certainty that *"means will not achieve the agreed upon goal"*.

Do not Resuscitate Orders (DNR)

In circumstances described above, "Do Not Resuscitate" orders signed by the attending physician/intensivist incharge can be placed in the medical case sheet of the patient based upon parental consent obtained regarding the interventions to be performed (such as cardiac compressions, endotracheal intubation, use of resuscitative drugs) or not to be performed in the event of deterioration of clinical condition of a child who has been previously agreed upon to be terminally ill. Such orders are NOT in practice in the Indian scenario, as these orders have no legal standing in the Indian courts of law.

In the Pediatric context justification for limitation and withdrawal of interventions are as follows: (EAC-RCPCH guidelines)[6]

1. The permanent vegetative state.
2. The "no chance" situation where there is expectation of imminent death despite aggressive treatment.
3. The "no purpose" situation where there is decrease in quality of life despite potentially extended survival.
4. The "unbearable" situation where in the face of progressive illness further treatment is more than can be borne.

In Indian legal system[7] there is no such legal provision to discontinue therapy (withdrawal) or withholding even if it is considered futile except in a brain dead patient.

Do not resuscitate status option does not exist. Therefore in our scenario "non escalation strategy" is used when a medical treatment of a particular condition is considered futile (Not adding any newer therapeutic modalities once the treatment is considered futile). Nature takes its course in such situations and the agony to the patient and the family may be prolonged with a continued treatment in PICU sometimes with the wish of the family and sometimes against the families wishes, due to nonallowance of the witholding or withdrawal of treatment, unless family wishes to take patient away against medical advice.

Assisted suicide and euthanasia are illegal in INDIA.

As mentioned above some of the families would take patients home "LAMA"(leaving against medical advice) when they recognize that the death is imminent or the treatment is futile. This process gets hastened in private hospitals due to escalating medical bills with no definite benefit in sight.

Most of such decisions are taken jointly by the family and physician team members. Unfortunately, in the Indian setup, it is still not a routine practice to involve nurses in these decisions although it is extremely important that as an active team member, the nurse be involved in all such meetings.

Indian society of critical care medicine (ISCCM) has recently developed guidelines for End of life care as it applies to the Indian scenario[8] recently published in Indian Journal of Critcal Care Medicine. Brief executive summary is listed as follows:

1. The physician has a duty to disclose to the capable patient or family, the patient's poor prognosis with honesty and clarity when further aggressive support appears non-beneficial. The physician should initiate discussions on the treatment options available including the option of no specific treatment.
2. When the fully informed capable patient or family desires to consider palliative care, the physician should offer the available modalities of limiting life-prolonging interventions.
3. The physician must discuss the implications of forgoing aggressive interventions through formal conferences with the capable patient or family, and work towards a shared decision-making process. Thus, he accepts patient's autonomy in making an informed choice of therapy, while fulfilling his/her obligation to provide beneficent care.
4. Pending consensus decisions or in the event of conflicts between the physician's recommendations and the family's wishes, all existing supportive interventions should continue. The

physician however, is not morally obliged to institute new therapies against his/her better clinical judgment.

5. The discussions leading up to the decision to withhold life-sustaining therapies should be clearly documented in the case records, to ensure transparency and to avoid future misunderstandings. Such documentation should mention the persons who participated in the decision-making process and the treatments withheld or withdrawn.
6. The overall responsibility for the decision rests with the attending physician/intensivist of the patient, who must ensure that all members of the caregiver team including the medical and nursing staff agree with and follow the same approach to the care of the patient.
7. If the capable patient or family consistently desires that life support be withdrawn, in situations in which the physician considers aggressive treatment non-beneficial, the treating team is ethically bound to consider withdrawal within the limits of existing laws.
8. In the event of withdrawal or withholding of support, it is the physician's obligation to provide compassionate and effective palliative care to the patient as well as attend to the emotional needs of the family.

ENDSTAGE PALLIATIVE CARE[9]

Once a child's medical diagnosis, prognosis and irreversibility of the problem is established and accepted by the medical team and the family, a care plan to ensure best comfort of the child should be formulated by the medical team in consultation with the parents. While measures to ensure adequate pain relief and adequate nutrition should take priority, psychological support to the child and family should also be given equal attention.

Nutritional Support

With the help of *dietetians*, with adequate nutritional assessment and assessment of caloric needs, nasogastric feeds, naso duodenal, nasojejunal feeds, or gastrostomy feeds (as applicable) should be instituted and continued preferably with involvement of one or both of the parents so that they can learn such techniques under supervision of a nurse. Continuing a childs nutrition and keeping the child's pain free are very fulfilling and satisfying experiences for parents in an otherwise desperate situation where loss of the child's life is imminent.

Pain Management

Patient controlled, or parent controlled analgesia (PCA pump technology) is now available for almost all patients (including small infants) who suffer from chronic pains any where in the body. Help of an anesthesia colleague should be sought in collaboration with the pediatric intensivist, as pain management itself is a distinct and fairly advanced superspeciality of anesthesia specializing in the use of regional anesthesia techniques, intra articular steroid injections, transcutaneous electrical nerve stimulation (TENS), analgesic patches, nasal narcotics, fentanyl lollipops and many other modalities that have become available. A detailed discussion of these modalities is beyond the scope of this article.

Psychological Support

Involvement of a clinical child psychologist in the palliative care of all children is important both for the child as well as for the family. Open discussions of the fears, care related issues, complaints as well as reassurances that best possible care is being delivered to the child keeps the feeling of guilt related to "fear of not doing enough for the child" away.

Children represent the dreams and hopes of their parents. Allowing time for goodbyes, visits and rituals permits the opportunity to form some cherished memories. Open visitations make the team's job easier, decrease parental anxiety, and increase the child's cooperativeness with procedures.

Bereavement and Grief[10,11]

Losing a child of any age can be one of life's most devastating losses.

Grief indicates the experience of one who has lost loved one to death.

Bereavement defines the loss to which the person is trying to adapt.

Through the process of grieving one learns how to cope with the future in spite of one's loss. How well one manages this affects one's quality of life and one's ability to relate to others. Mourning is an emotional process that occurs after a loss, and it is an essential and painful healing process, which is achieved through a series of tasks that are:

1. Facing Reality
2. Experiencing the pain of grief
3. Adjusting to the new reality
4. Re-investing in the future and moving on with life.

Grief can manifest itself in different forms which can be broadly classified under four categories- feelings, physical sensations, cognitions and behaviors.

Feelings associated with grief and bereavement are:

- **Sadness-** It is the most common feeling found in the bereaved. This feeling may manifest by crying behavior. Crying is a signal that evokes a sympathetic and protective reaction from others and establishes a social situation in which the normal laws of competitive behaviors are suspended.
- **Anger-** Parents of a dying child may frequently experience feelings of anger. The feelings of anger may come from two sources– first from a sense of frustration that nothing can be done to prevent the dying child and second, from a kind of regressive experience that occurs after the loss of someone close. In the loss of any important person there is a tendency to regress, to feel helpless, to feel unable to exist without the person, and then to experience the anger that goes along with the feelings of anxiety. It is important for the bereaved person to identify the anger and target it toward the deceased appropriately. This can be done either by displacement or blaming others. People for example, may blame the physician for the death. If someone can be blamed, then that person is responsible and, hence, the loss could have been prevented. The anger may also turn inward against the self. In severe cases the person may develop severe depression and suicidal behavior.
- **Guilt and Self-reproach-** Feelings of guilt can be manifested over something that happened or something that was neglected around the time of death. The guilt can be irrational and in some cases real also where the person has done something to cause the death. Authors have posited five types of guilt that bereaved parents may experience. The first is cultural guilt, society expects parents to be guardians of their children and to take care of them. The death of a child is an affront to this social expectation. Causal guilt may be experienced if the parent feels responsible for death of child through some real or perceived negligence. Moral guilt is characterized by the parent feeling that the death of the child was due to some moral infarction in their present or past life. Survival guilt may also be found among bereaved parents. Why did my child die and I am still alive? Finally, recovery guilt is experienced when parents feel guilty when they move through their grief and want to get on with their life. They believe that such recovery somehow dishonors the memory of their dead child and that society may judge them negatively.
- **Anxiety-** This feeling of anxiety can range from a light sense of insecurity to a strong panic attack. Anxiety may result from two sources. First, the survivor fear that they will not be able to take care of themselves on their own and second, anxiety relates to a heightened sense of personal death awareness.
- **Loneliness-** Loneliness can accompany after the loss of loved one. Researchers distinguish between emotional loneliness and social loneliness. Social support can help with social loneliness but does not mitigate against emotional loneliness due to broken attachment.
- **Fatigue-** Fatigue may be experienced as apathy or listlessness. It is self-limiting and may be a clinical sign of depression.
- **Helplessness-** The feeling of helplessness makes the event of loss a very stressful experience.
- **Shock-** Shock occurs mostly in the case of sudden death.
- **Yearning-** Yearning or pining is a normal response to loss. When it diminishes, it may be a sign that mourning is coming to an end. When it does not come to an end, it may be a clinical sign indicating traumatic grief.
- **Emancipation-** It is a normal feeling after death.
- **Relief-** Feeling relieved after the death of loved one, particularly if the loved one suffered a lengthy painful illness.

- **Numbness**- This feeling of numbness is often experienced early in the grieving process, usually right after the learning of the death. Researchers believes that feeling of numbness or blocking of sensation act as a defense against what would otherwise be overwhelming pain would seem to be extremely normal.

Physical sensations experienced during grief and bereavement:
Some of the commonly reported physical sensations include: Hollowness in the stomach, tightness in the chest and throat, oversensitivity to noise, a sense of depersonalization, breathlessness, weakness in the muscles, lack of energy and lastly dry mouth .

Cognitions associated with grief and bereavement: Some of the cognitions that may prevail during the grieving process are-disbelief, confusion, preoccupation, sense of presence, hallucinations and depression. The feelings of depression may be regarded as normal by the bereaved individual. Depression overlaps with bereavement but is not the same. Freud believed that in grief, the world looks poor and empty while in depression, the person feels poor and empty.

Behaviors associated with grief and bereavement: There are a number of specific behaviors that are associated with normal grief reactions. These can range from sleep and appetite disturbances, absentminded behavior, social withdrawal, dreams of the deceased, avoiding reminders of the deceased, searching and calling out, sighing, restless overactivity, crying, and treasuring objects that belonged to the deceased.

Process of Grieving

The grief process has been described as falling into several phases which are-

- **Shock and denial (minutes, days, weeks).**
- Disbelief and numbness.
- Searching behaviors: pining, yearning, protest.
- **Acute anguish (weeks, months).**
- Waves of somatic distress.
- Withdrawal.
- Preoccupation.
- Anger.
- Guilt.
- Lost patterns of conduct.
- Restless and agitated.
- Aimless and a motivational.
- Identification with the bereaved.
- **Resolution (months, years).**
- Have grieved.
- Return to work.
- Resume old roles.
- Acquire new roles.
- Reexperience pleasure.
- Seek companionship and love of others.

The grief experience may be different for each parent due to their varied relationship with the child and their own different coping styles. Each parent needs to understand his or her own way of expressing grief as well as their partner's grieving style. There are gender differences that play out in the expression of grief. These gender role expectations are part of the socialization process of our society and its culture. Studies reveal that men are more likely to fear the consequences of emotional expression in social context. For men, the open expression of emotion is often discouraged. Bereaved fathers face more difficulty. First, fathers are given little social support while they are expected to be a major source of support for their wives, children and other family members. Second, fathers are confronted with the culturally idealized notion that grief is best handled through expressiveness, while at the same time they need to control such frightening and overwhelming expressions of grief. These conflicts between social and personal experience can lead men to feel frustration, anger and aloneness in grief.

Bereaved parents face two issues: (1) learning to live without the child, which includes a new form of interacting with social network and (2) internalizing an inner representation of child that brings comfort Thus the various tasks of mourning can be described where first task for the parents will be to struggle between belief and nonbelief. On the one hand parents know that the child is gone and on the othe hand they don't want to believe it. Second task will be to process feelings associated with the loss such as anger, guilt and self blame and finally the las task will be to find some kind of meaning from th death of their child.[34] There are many ways of findin meanings for example some may find meaning i adherence to religion.

INTERVENTIONS

From the above discussion it becomes clear that staying in a hospital is a stressful experience for the patient as well as the family. It is important for healthcare professionals to develop some awareness of the sources of stress as well as to work out on these in order to reduce them. It is important to understand the parent's perception of their own needs while they are staying in a hospital. Several studies[1] have been undertaken to identify parents' own perceptions of their needs for support while their children are in hospital. Some of the needs that were identified are:

- To receive accurate information about their child's condition that is honest, exact, understandable, ongoing, freely offered, consistent, well-timed and comprehensive.
- To have ready access to their child and have meaningful participation in their care and be recognised as important to their recovery
- To have a trust in the staff and feel that they care about the parents as well as the child.
- To be assured that the child is receiving the best care possible.
- To receive support from their own social networks (including relatives, friends and workplace colleagues) and opportunities for the direct involvement of grandparents and siblings (include somewhere for the latter to play).

Presence of the Family While Withdrawing Life Support Systems

Frequently families want to be present with the child at the time of death or wish to hold the child in their lap when life support is being terminated. Ask parents if they have such desires. Fears about heightened parental distress during such events are exaggerated. On the contrary, a majority of family members regret not having stayed with their child at the time of death.[12]

Spiritual Beliefs, Rites and Rituals

Spiritual beliefs strongly influence the existential issues of life, death and suffering. Parents with strong spiritual beliefs seem to resolve their grief more rapidly and completely after the death of a child.[13] Family members find great comfort when they are given an opportunity to perform religious rituals in the PICU[14] and norms need to be established in each PICU that allows the conduct of ceremonies by religious groups within limits decided by hospitals.

As far as the communication goes,following recommendations pertain to medical teams responsibility as it applies to the PICU patients who is dying and his family members.[15]

Strategies to Enhance Communication

1. It is important to introduce everyone who is involved in the care to the family. This will help in reducing the unfamiliarity surrounding the hospital and also the people working in it.
2. It is important to meet the family quite frequently in case of emergency as this will reduce the fear and anxiety of the family members.
3. Indicate members directly involved in the care of their child and how they may be contacted.
4. It is again very necessary to ensure whether whatever is being communicated have made some sense to the receiving family or not. So it becomes important to avoid scientific jargon and use simple language even with educated individuals.
5. One should anticipate and encourage questions from the parents.
6. It is important to frequently stop in order to check whether the family has kept pace with the rate of delivery of information.
7. Explaining each procedure/therapy in detail-expectations, possible side effects and other consequences will help the family in getting a complete picture of the child's problem.
8. It is important to again provide some space to the parents where they can express their own thoughts, fears and doubts. This can be done by encouraging suggestions from parents *e.g.*, their perception of what the child requires and discussing the appropriateness of each.
9. Communication is vital while working with dying children and their families. Family members who had been accurately informed about expected events around the end of life were often found to experience less anxiety and expend less effort in trying to cope with their loss. Frequent,

accurate and truthful discussions with parents alleviate the sense of uncertainty and foster confidence both in parents as well as the families.

Breaking Bad News[16]

Inform family of need to discuss important information.

Provide an opportunity for supportive friends or family to be present when the information is shared.

Tell the news in a private setting, with the physician, nurse and social worker present. Bring the family (generally parents without the child first, depending on the relationship and preferences) to a private room. If appropriate and desired by the family, assist them in telling their children (patient and siblings) afterwards.

Sit down near the family, not across a table. Do not stand. Look the family members in the eye (if culturally appropriate) to engender trust. Ask them to tell you about their child and about any consistent values of the child and about the things that give him or her pleasure. Ask how much they want to know about his or her medical condition and prognosis. Ask them what they understand is happening. Clarify misconceptions, Ask the family to explain what they understood was said. Clarify misconceptions. Then, solicit additional questions.

Be unhurried. Don't look at your watch. Ideally, members of the interdisciplinary team participate as full members during the family conference. Bring trainees to the family meeting. It keeps trainees informed so that unnecessary and often damaging miscommunications do not occur. However, do not overwhelm the family with white coats. Have trainees take turns in attending family meetings.

Be specific. The physician should present the options, including a description of life-sustaining treatments, the child's current status, the chance of survival, the probability of full recovery (and the probability of significant disability), and the possible effects of the child's long-term survival on the family. Be sure to explain the benefits and burdens (including prolongation of suffering) of each potential care plan, the potential reversibility or irreversibility of the conditions being treated, the time frame of reevaluation, the projected future quality of life, and the comfort measures available if the ICU interventions are curtailed or discontinued. Give reassurances that, if life-sustaining medical interventions are discontinued, the child will continue to receive attentive care for the relief of symptoms; describe the procedures to be undertaken, including the opportunities to observe important customs and rituals and the visitation allowances.

HELPING PARENTS FACE THE DEATH OF THEIR CHILD[17,18]

Communicate

Listen attentively.
Find out what the family knows and what they want to know.
Use language that family members can understand.
Call the child by name.
Use silence as an ally but watch for signs that parents need to talk.
Encourage questions.
Do not offer platitudes.
Do not automatically offer tissues.

Facilitate Family Grieving

Offer a private place for the family to retreat.
If death occurs, allow the family time with the child after the death.
Encourage involvement of siblings.
Preserve memories of the child: last height, weight, lock of hair, hospital name band, plaster of Paris hand-or footprint, picture of the child, child's blanket and clothes in a plastic bag (to preserve scent).
Provide specific information about how the needs of siblings can be met.
Provide pamphlets for family members and friends to give them tips about how to help the parents.

Rights of Parents When a Baby Dies

To be given the opportunity to see, hold and touch their baby at any time before and/or after death within reason.
To have photographs of their baby taken, and made available to the parents or held in security until the parents wish to see them.
To be given as many mementos as possible, e.g. crib card, baby beads, ultrasound and/or other photos, lock of hair, feet and handprints, and record of weight and length.

To name their child and bond with him or her.

To observe cultural and religious practices.

To be cared for by an empathetic staff, who will respect their feelings, thoughts, beliefs, and individual requests.

To be with each other throughout hospitalization as much as possible.

To be given time alone with their baby, allowing for individual needs.

To request an autopsy. In the case of miscarriage, to request to have or not to have an autopsy or pathology exam as determined by applicable law.

To have information presented in terminology understandable to the parents regarding their baby's status and cause of death, including autopsy and pathology reports and medical records.

To plan a farewell ritual, burial, or cremation; in compliance with local state regulations and according to their personal beliefs, religious or cultural tradition.

To be provided with information on support resources, which assist in the healing process, e.g. support groups, counseling, reading material, and perinatal loss newsletters.

SUPPORTING GRIEVING FAMILIES[19,20]

General

Stay with the family; sit quietly if they prefer not to talk; cry with them if desired

Accept the family's grief reactions; avoid judgmental statements (e.g. "You should be feeling better by now")

Avoid offering rationalizations for the child's death (e.g. "You should be glad your child isn't suffering anymore")

Avoid artificial consolation (e.g. "I know how you feel," or "You are still young enough to have another baby")

Deal openly with feelings such as guilt, anger, and loss of self-esteem

Focus on feelings by using a feeling word in the statement (e.g. "You're still feeling all the pain of losing a child")

Refer the family to an appropriate self-help group or for professional help if needed

At the Time of Death

Reassure the family that everything possible is being done for the child, if they wish lifesaving interventions

Do everything possible to ensure the child's comfort, especially relieving pain

Provide the child and family the opportunity to review special experiences or memories in their lives

Express personal feelings of loss and/or frustrations (e.g. "We will miss him so much," or "We tried everything; we feel so sorry that we couldn't save him")

Provide information that the family requests and be honest

Respect the emotional needs of family members, such as siblings, who may need brief respites from the dying child

Make every effort to arrange for family members, especially parents, to be with the child at the moment of death, if they wish to be present

Allow the family to stay with the dead child for as long as they wish and to rock, hold, or bathe the child

Provide practical help when possible, such as collecting the child's belongings

Arrange for spiritual support, such as clergy; pray with the family if no one else can stay with them

After the Death

Initiate and maintain contact (e.g. sending cards, telephoning, inviting them back to the unit, or making a home visit)

Refer to the dead child by name; discuss shared memories with the family

Discourage the use of drugs or alcohol as a method of escaping grief

Encourage all family members to communicate their feelings rather than remaining silent to avoid upsetting another member

Emphasize that grieving is a painful process that may last for years

SUMMARY

Some of the common sources of stress in a hospital are unfamiliar hospital setting, restriction in one's movement, losing one's parental role, as well as economic, personal and social worries. The amount of stress experienced by the caregivers may also vary according to the physical condition of the child. If the child is critical and about to die then the amount of stress experienced by the parents would be more as compared to a child who may get well in few days. It is important to understand the manifestations of grief and bereavement at this point. Communication is an art. It is a necessity for all members of the medical team taking care of sick children at risk of dying, to adequately communicate with the families to keep the satisfaction level high, as well as to avoid any later legal consequences due to miscommunication or noncommunication between the healthcare team and the patient family. Most parents are able to cope with their feelings of loss but some have trouble resolving their feelings about the loss. It is necessary to understand the needs of the grieving parents and develop some effective strategies to deal with it. The main focus of these strategies should be to provide assurance, hope and support in order to deal with the anxiety, stress and discomfort experienced. If the parents are facing trouble in resuming a normal life then seeking psychological help from a mental health professional is required.Palliative care is an entire process aimed to keep the child comfortable and nourished through the end stage of life.Legal provisions related to end of life issues are important to consider while taking end of life decisions in meetings with the family members of a dying patient,or a patient recieving futile medical therapy with no benefit in sight.Most conflicts during stressful times can be resolved through regular communications in family and medical team meetings.

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CHAPTER

Limitation of Life Support in the Pediatric Intensive Care Unit: Ethical Issues Relating to End of Life Care

RK Mani, Praveen Khilnani

Intensive care has come to be associated with hightech, aggressive and often risk-filled medical care. Although critical care has expanded the scope of modern medicine, its mortality remains significant at 8.5-36 percent[1,2] depending upon data from the developed or the developing countries respectively. Aggressive treatment even in the face of hopeless prognosis has become common place in intensive care units (ICUs). While in an earlier era, the terminally ill passed away amidst their family at home, death now has become "medicalized"[3] with the patient cut off from his loved ones in his final hour. Death of a child now often takes place in a pediatric intensive care unit (PICU) surrounded by invasive lines, devices and machines.

Not surprisingly, doctors are often perceived as being insensitive to the wishes of the patient and his family when medical treatment is not beneficial in the real sense. In the care of infants and children this issue of what is a good life gets even more challenging when the neurological outcome involves possible vegetative state and parents wish everything done in the PICU.

We should therefore ask ourselves where to draw the line in applying life support methods in order that we do not unnecessarily extend the natural process of dying. Ethics do not require that we apply technology indiscriminately "to save life at all costs", but rather to act in the best interests of the child and his family.[4] The following chapter addresses the general issues of end of life care applying to any intensive care unit, regardless of the age. Specific issues relating to the pediatric intensive care are also addressed wherever applicable.

Definitions of Categories

In order to avoid futile medical care various practices limiting life support have been proposed (Table 94.1).

Table 94.1: Definitions of terms used during end of life care issues

Full resuscitation	Aggressive ICU management up to and including full resuscitative attempts.
Withholding of resuscitation (DNR)	Aggressive ICU management up to, but not including attempts at CPR. A patient who is resuscitated only to die later without CPR is considered to have had resuscitation withheld only if more than 24 hr elapsed from the successful resuscitation.
Withholding of life support	The considered decision not to institute a medically appropriate and potentially beneficial therapy with the understanding that the patient will probably die without the therapy in question.
Withdrawal of life support	The cessation and removal of an ongoing medical therapy with the explicit intent not to substitute an equivalent alternative treatment. It is fully anticipated that the patient will die following the change in therapy.
Physician-assisted suicide	A medical doctor provides patients with means to kill themselves.
Euthanasia	The intentional killing of a patient by the direct intervention of a doctor, ostensibly for the good of the patient or others.

Standards of Practice

ICU practices were studied prospectively by the *Support* group of investigators.[5] This landmark study to understand the Prognosis and Preferences of Outcomes and Risks of Treatment showed clearly that seriously ill patients get more expensive treatment and have longer ICU stay. They often die in undesirable states such as coma and ventilatory support. It has also brought out the fact that intensivists are applying treatments on patients during their end of life that they would not prefer for themselves or their children.

Since the *support* revelations the practices in ICUs are clearly changing. In an extensive survey of the end-of-life care in US ICUs, Pendergast et al[1] found data that challenge the observations of the *Support* study. They found that in 48 percent of ICUs in the US limitation of life support is the predominant practice.

Out of 5910 deaths, 74 percent had been on a life-limiting care (Table 94.2). This figure is an aggregate with a wide variability in practices in different institutions. However, the median practice was to limit life support in 70 percent of deaths. 48 percent were by withdrawal or withholding of life support and only 28 percent received full CPR.

In contrast, in one leading hospital in India (Table 94.3) only 22 percent had life-limiting management and probably this reflects the general trend. Do not resuscitate (DNR) orders were written with family's consent in only 4 out of 109 deaths. LAMA (left against medical advice) is a situation peculiar to this part of the world. We have regarded these as withdrawal of treatment unilaterally by the patient's family. All of these were due to financial constraints.

Table 94.2: Pendergast study

Total ICU admissions	74,502
Total ICU deaths	6,303 (8.5% mortality)
Brain deaths	393 (6.2% of deaths)
Patients facing end-of-life decisions	5,910
Full resuscitation	1,544 (26%)
Withholding of resuscitation (DNR)	1,430 (24%)
Withholding of life support	797 (14%)
Withdrawal of life support	2,139 (36%)

From: Pendergast TJ, et al. AJRCCM 1998;158:1163-67.

Table 94.3: Data from a tertiary care Indian Hospital March-Aug 2002

Total admissions	429
Deaths Actively managed	84 (20%)
Limiting life support	17 (3.6-22%) of deaths
DNR	4
LAMA	13
Brain Death	2 (Life support withdrawn)

It tells the tragic story of the enormous financial and emotional burdens that the family has to endure in the context of critical illness, in view of majority of patients or parents bearing the cost of medical care as an out of pocket expense. Families are often financially torn and despite wishing to save the critically ill child or the family member, they do not get any guarantees from the treating doctor regarding the outcome. Consequently this tremendous financial stress with an uncertainty of outcome leads to LAMA.

Quality of Care

There are misgivings about writing DNR orders or a strategy of limiting life support that the patients thus categorized may receive less medical attention and their care may be suboptimal. On the other hand, they may also be spared of the unwarranted interventions that a full-fledged management would entail.

In the study by Hall et al[6] which compared the treatment of patients when life supporting treatment was or was not withdrawn, clear differences were evident. Those in the withdrawal or withholding group were older, received fewer interventions before death (mechanical ventilation, inotropic

Table 94.4: Use of support measures at the time of death

	Life Support withdrawn		
Support measure	*Yes (n=138)*	*No (n=36)*	*P Value*
Inotropic agents	21	36	< 0.001
$FiO_2 > 0.21$	81	36	< 0.001
Concurrent medications	24	35	< 0.001
Nutrition (enteral or parenteral)	22	9	0.206
Dialysis (within 12 h of death)	2	4	0.014

Source: Hall RI, et al. Chest 2000;118:1424-30.

Table 94.5: Cumulative 12-h dose in milligrams of medications in patient dying when life support was or was not withdrawn

	Life Support withdrawn				
Drug (mg)	*Yes*		*No*		*P Value*
Morphine	32	(1-698)	6	(2-202)	0.007
Fentanyl	0.500	(0.030-6.600)	0.237	(0.025-0.450)	0.203
Diazepam	20	(3-155)	21.5	(5-100)	0.965
Midazolam	10	(1-593)	5	(2-50)	0.206
Lorazepam	5.5	(1-60)	1	(1-2)	0.006
Propofol	1673	(113-61,308)	800	(10-1,741)	0.080
Pancuronium	13	(8-44)	18	(6-20)	0.333
Vacuronium	13	(4-554)	20	(4-34)	0.096

Source: Hall RI, et al. Chest 2000;118:1424-30.

agents, dialysis), (Table 94.4) but received more sedatives and narcotic analgesia (Table 94.5).

Cost Reduction

Total health care costs in the US is estimated to be 14 percent of the GDP (Gross Domestic Product) and a disproportionate amount is spent on critical illness in the elderly population.[7] Limitation of life support may therefore be expected to result in considerable fiscal efficiency.

Critical care is very expensive and on average more expenses are incurred on patients who die than on those who survive. Life sustaining treatment is often not cost-effective and data on ICU practices clearly indicate that standards of care have not been defined. Therefore, there would be plenty of room to apply cost reduction strategies in the ICU.

However, as observed by Luce and Ruberfeld,[7] restrictions on life-sustaining treatment may not yield significant cost savings. In the US this is due to fixed costs and contractual arrangements. In the Indian context the cost benefits are real since in the most part, expenses are borne entirely by the patient. In India an increase in bed strength does not necessarily mean an increase in expenses to the hospital.

Ethical and Legal Issues Relating to Life Support Limitation

The practice of withholding or withdrawing life support in the ICU and administering palliative care is supported by the ethical principles of autonomy, beneficence and non-malefiscence.

Our understanding of the laws governing these practices in the US and elsewhere may contribute to evolving legislation to suit our own requirements.

Autonomy

The principle of the right to self determination led to the concept of informed consent and informed refusal. The principle holds that treatment may not be initiated without the approval of patients or their surrogates except in emergency situations and that the patients or their surrogates may refuse all therapies. American law requires that there should be clear and convincing evidence of the patient's wishes. This is achieved by Advance Directive or Will.[8]

In the absence of Advance Directive the surrogates (family members) may act on his behalf. The problem of Will is that it is rarely available and the patient may change his mind or may not have visualized his present situation. In France where the State does not recognize the right of surrogates to represent the incompetent patient, the doctor is given the responsibility of acting in his best interests.[9] Thus, in France the principle of benefiscence takes precedence over that of autonomy. This is often dubbed as "paternalism".[10]

In the case of Quinlan (1976)[8] the New Jersey Supreme Court held that the patient had the right to refuse mechanical ventilation and, because she was vegetative and could not exercise that right directly, her parents could act as surrogates for her.

In the case of *Barber* (1983)[8] the California Court held that physicians charged with murder had not committed an unlawful act, when, with the permission of the family, they removed nutrition and hydration from a comatose patient.

The issue of withholding and withdrawal of life support was first addressed by the US court in the *Cruzan* case (1990).[8] The Cruzans wanted a feeding tube removed from their vegetative daughter. In Missouri, where they lived, the court required specific evidence that an incompetent person would want treatment withdrawn. The court required "clear and convincing" evidence of the patient's wishes, which limits the role of surrogates in case the patient is incompetent. The reliability of surrogates as representing truly the patient's wishes has been questioned in the UK and in France it is acceptable practice for the physician to act unilaterally in a "paternalistic" manner. Nevertheless, in the *Cruzan* case later the court acknowledged the right of a competent patient to forgo treatment even if it meant that this would result in his death. In most states of the US, surrogates' requests are honored despite the *Cruzan* judgment.

The Concept of Futility

Doctors often cite futility of continuing therapy as justification to withhold or withdraw it. Since the perceptions of the patients or their surrogates may be different from the doctors, these have been modified to indicate the so-called "physiologic futility'.[11] Even with this term value judgments are inevitable as few things are of absolute certainty in clinical practice. For example, in writing DNR orders it would be impossible to be sure of an immediate as opposed to eventual physiological futility of CPR except in the circumstances such as cardiac rupture or severe outflow obstruction. Using this principle physicians have been found to act unilaterally. The position of the US courts has been rather ambiguous in this regard.

In the *Baby K* case (1994)[12] when the court was asked to approve in advance a physician's decision to withhold life-sustaining treatment, the Court refused to do so. On the other hand, in the case of *Gilguun* (1995)[8] the courts were reluctant to punish doctors after they issued a DNR order and removed the ventilator from a patient over the objections of the patient's daughter. In the *Wendland* case,[13] the wife wanted to remove the feeding tube from her husband who had been comatose for 2 years. Her husband's mother, however, went to court to block the plan. The court thus recognizes a hierarchy of proxy where its ruling supports one who is in favor of protecting life. It also points to the difficulties in asking the surrogates to take decisions, as the dilemma of disagreement within the family members may arise.

The trend in futility cases is that while courts do not permit life support limitation prospectively on appeal from doctors, they tend to defend decisions to limit life sustaining therapy when they are made within acceptable professional standards.[8]

Despite the outcome of these cases we must eschew the practice of taking unilateral decisions on what is evidently a sensitive matter. This trend has become evident in France as well where there are less legal obligations to do so.[9] Decisions are to be made jointly with the patients or surrogates. This respects their right of self determination, and avoids misunderstanding and conflicts that may lead to litigation. The doctor may in his discussion with the family play the role of an informer or a counsellor.[11] He should allow time for the family to accept the realities and for a consensus decision to emerge through a cooperative process. The physicians should clear the air of wrong notions, prejudices and misinformation. Often a period of de-escalation of aggressive treatment enables the family to come to terms with the realities and agree to a formal consent for withdrawal or withholding of life support.

Legal Aspects of Palliative Care

In the cases of *Glucksberg* (1997) and *Vacco* (1997) the US Supreme Court confined its approval of forgoing life sustaining treatment and provided guidelines for administering palliative care.[8] These cases dealt with the constitutionality of the laws prohibiting physician-assisted suicide in the states of Washington and New York. Since there are laws prohibiting suicide, and there are legitimate fears of misuse, physician-assisted suicide continues to be illegal. However, the Court acknowledged the right of patients to receive adequate pain relief during the dying process.

The Double Effect

The patients' access to palliative care may be limited by the principle of nonmalefiscence as it does not permit physicians to intend potentially harmful effects. The US Supreme Court distinguished assisted suicide from palliative care by accepting the principle of "double effect". Quill and associates[14] described it and distinguished between intended and unforseen effects. Giving of analgesics and sedatives are justifiable if their bad effects are not intended, and there are no less risky ways of relieving suffering.

Terminal Sedation

The US Supreme Court also sanctioned the practice of terminal sedation, in which patients are rendered comatose and then may have nutrition and hydration withdrawn. Though this issue is contentious, the Court allows the practice if it is based on informed consent.[8]

Physician Assisted Suicide and Euthanasia

In physician assisted suicide (PAS) the actual killing drug is self-administered with help from a physician and in euthanasia the physician himself administers the lethal dose. The much-debated practice has received legal sanction in very few regions of the world.[15] The first legal sanction of euthanasia (the Northern Territory Rights of the Terminally Ill Act 1995, Australia) was repealed in 1997. The Netherlands never had legal sanctions but because of a "Tolerant Judiciary" the practice of euthanasia is common among Dutch physicians. In the state of Oregon in the US, Death with Dignity Act was passed allowing PAS. Even in this state the practice is not widespread.[16]

Drawbacks in the Current Strategies

The dominance of the principle of autonomy over that of beneficence often leads to inappropriate treatment. The physician's role is also hampered by his inability to exercise his judgement in the best interests of his patients. Rejecting the idea of futility, the patient's family often impose unreasonable demands on him. The doctor often finds himself in a moral dilemma without adequate legal safeguards against misinformed decisions by the families. In this part of the world his problems are compounded by the need to ration resources and the moral obligation to protect families from financial ruin. He is also subjected to societal pressures that erodes his self esteem as a professional.

The Indian Scenario

Unlike in the US, in India legal opinion and legislation relating to end-of-life care is scarce. It is rather disturbing that there is no clearly stated legal opinion regarding discontinuation of life support systems even in brain dead patients.[15]

In India Article 21 provides the right to life. However, the concept of autonomy is still weak and even the right to live a dignified life is not adequately explored for the purpose of end-of-life care.

The Transplantation of Human Organ Act (1994) defines brain death. There have been a paucity of cases dealt with by Indian courts in the matter of terminal illness. In the *P. Rathinam* vs *Union of India,* 1994,[17] the Supreme Court conceded that in the case of terminal illness, attempts to hasten death may be viewed as acceleration of a dying process already started. The Court acknowledged that "a person cannot be forced to enjoy the right to life to his detriment, disadvantage or dislike."

However, in the *Gian Kaur* vs *State of Punjab*[18] the Court categorically stated that the right to live cannot be interpreted to include the right to die an unnatural death curtailing the natural span. The judge declared that the plea to support the view of permitting termination of life in cases of a dying man, who is terminally ill or in persistent vegetative state, to reduce the period of suffering during the process of certain natural death, is not available to interpret Article 21.

Our religious texts glorify the act of suicide as "mahaprasthana" (great departure).[19] Voluntary starvation was considered the befitting conclusion of a hermit's life and this was prevalent among the Jain ascetics as well. However, the position of the apex court in this regard is different. The natural corollary of the judgement in the *Gian Kaur* case is that it disallows the concept of euthanasia as it violates article 21 of the constitution. It also reaffirms that abetment to suicide is a punishable offence while attempted suicide is viewed more compassionately.

The Indian Penal Code declares attempt to suicide or abetting to suicide as illegal. The sale of morphine sulfate is also illegal in most states.[15]

Lakhs of rupees of compensation can be claimed today without a penny being tendered as court fee in consumer disputes redressal fora. The deterrence of an *ad valorem* court fee is no longer there and consequently an increasing number of professionals are being involved in interminable cases. The problem becomes more complicated in grey areas where there is a legal penumbra. Without proper legal definitions of rights often the doctor is called upon to take on-the-spot decisions on legal conundrums which have required decades of deliberations in the Courts.

The Impact of Socio-cultural Factors in India

The predominant factor that impacts on decision-making in the ICU is the unbearable financial burden that it entails. As a consequence the family goes through complex emotional upheaval. The doctor is often a witness to the feelings of guilt, fatalism and denial that the family would experience. The family tends to nurture false hopes in the face of hopeless prognosis that is supported by misinformation. There is also the unwanted intrusion of alternative systems of medicine that only helps to reaffirm entrenched prejudices.

Above all, the legal process is too slow to allow legal interventions prospectively in a patient's management where required. Redressal has been expedited by consumer courts, but they have not been used to address issues related to end-of-life care. Generally Indian sensibilities rarely allow withdrawal of support and withholding may be more acceptable.

Emotional Support to the Family

Providing emotional support to the patient's family is an essential part of the responsibilities of the treating team. In a multicentre study conducted in France,[20] the needs of the ICU patients families were evaluated. The important predictors of family satisfaction included absence of contradiction in information given by caregivers, information provided by a junior physician, nurse to patient ratio < 3, help from the patient's family doctor and sufficient time spent giving information.

In another study looking at parental perspectives on end-of-life care in the pediatric ICU,[21] parents were found to place the highest priority on the perception of their child's pain, the quality of life and the likelihood of getting better when considering withdrawal of life support. A questionnaire revealed that parents depended mainly on critical care practitioners for decisions-making and emotional support. Holding a dying child in the mothers arm even with all the tubes and lines is possible and should be encouraged if desired by the family. Compassionate and supportive behavior towards the family, by the medical staff, nurses, and treating doctors goes a long way despite a poor prognosis or poor outcome. Non-communication, mis-communication, indifferent or rude behavior towards the family members should be avoided at all costs to prevent outbursts related to frustration, anger and possibly future litigation. Documentation of all patient related information and discussions with the family is as important as is actual delivery of compassionate care. Training of the pediatric intensivist must include a thorough discussion regarding end of life care issues, brain death, organ procurement and most importantly dealing with the families in a compassionate way regardless of the patient outcome.[22,23]

CONCLUSIONS

An appraisal of the ethical issues in critical care clearly urges us to apply intensive care with humanity and compassion. It is evident that setting appropriate goals and strategies in end-of-life care and in children with poor prognoses is as important as other skills in critical care. We need to respect the choices and the emotional needs of the child and his family. Our duties must include providing information, balanced interpretation of results and counseling of the family to enable them to take rational decisions. In consonance with the principle of autonomy, we should always take informed consent from the family (in case of minors and comatose patients) for withholding or withdrawing support including DNR orders. Our strategy in end-of-life care should be unambiguous and we should ensure that there is consensus among all the professionals (including the primary doctor and the primary nurse) involved in the patient's care. Our duties are not only towards the child but also to the families who look to us for emotional support and rational decisions to avoid unnecessary financial (particularly in uninsured self-paying families) and emotional burdens. Training of the pediatric intensivists to include this issue in the training curricula of the newer and developing training institutions is very important.

Finally, the medical community must work towards evolving legislation appropriate to Indian conditions.

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APPENDIX

Guidelines for limiting life-prolonging interventions and providing palliative care towards the end of life in Indian Intensive care units, February 2005: Executive summary

Committee for the Development of Guidelines for limiting life-prolonging interventions and providing palliative care towards the end of life: Indian Society of Critical Care Medicine.

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ABSTRACT

Purpose: To minimize inappropriate treatment and optimize comfort care for terminally ill patients in Indian intensive care units by standardizing the process of forgoing life support. It is also to define the ethical standards of physician-patient relationship in the context of critical care in India.

Evidence: Review of recently published literature on the subject. Available empirical data from critical care practice in India were sparse. The terms for search were: end-of-life care; withdrawal and withholding; intensive care; terminal care; medical futility; ethical issues; palliative care.

Method: Proposals from the Chair were debated and recommendations were formulated through a consensus process. The process took into account the guiding ethical principles and clinical practices elsewhere in the world, and incorporated the socio-cultural and legal perspectives unique to this country.

Guidelines

1. The physician has a duty to disclose to the capable patient or family, the patient's poor prognosis with honesty and clarity when further aggressive support appears non-beneficial. The physician should initiate discussions on the treatment options available including the option of no specific treatment.
2. When the fully informed capable patient or family desires to consider palliative care, the physician should offer the available modalities of limiting life-prolonging interventions.
3. The physician must discuss the implications of forgoing aggressive interventions through formal conferences with the capable patient or family, and work towards a shared decision-making process. Thus, he accepts patient's autonomy in making an informed choice of therapy, while fulfilling his/her obligation to provide beneficent care.
4. Pending consensus decisions or in the event of conflicts between the physician's recommendations and the family's wishes, all existing supportive interventions should continue. The physician however, is not morally obliged to institute new therapies against his/her better clinical judgment.
5. The discussions leading up to the decision to withhold life-sustaining therapies should be clearly documented in the case records, to ensure transparency and to avoid future misunderstandings. Such documentation should mention the persons who participated in the decision-making process and the treatments withheld or withdrawn.
6. The overall responsibility for the decision rests with the attending physician /intensivist of the patient, who must ensure that all members of the caregiver team including the medical and nursing staff agree with and follow the same approach to the care of the patient.
7. If the capable patient or family consistently desires that life support be withdrawn, in situations in which the physician considers aggressive treatment non-beneficial, the treating team is ethically bound to consider withdrawal within the limits of existing laws.
8. In the event of withdrawal or withholding of support, it is the physician's obligation to provide compassionate and effective palliative care to the patient as well as attend to the emotional needs of the family.

INTRODUCTION

> *"Dying can be a peaceful event or a great agony when it is inappropriately sustained by life support".*
>
> *Roger Bone*[1]

In the context of critical care, the physician's approach to the patient has three dimensions: medical, ethical and legal. This is because critical care involves the application of life-supporting interventions.

Death is common place in the critical care unit. The dying frequently die in critical care units: it is estimated that one in five Americans die using intensive care.[2] For many, life- support interventions have not helped to mitigate their suffering, but have rather added the agony and burden of a prolonged dying process. Death, which we all wish to be peaceful and to occur in the presence of loved ones, has become artificial, away from the family surrounded by the paraphernalia of modern critical care. Prolonged and futile life support has undoubtedly imposed enormous economic strains on patients and families. Potentially salvageable patients can be deprived of ICU care when scarce beds and resources are consumed in search of cure where death appears inevitable.

Where critical care is unlikely to restore patient to a meaningful existence, what is the responsibility of the physician?

In today's world limitation of life-supporting interventions is being increasingly practiced, as physicians realize that the mission of intensive care includes the avoidance of inappropriate use of aggressive interventions.[3] In the US and in Europe withholding or withdrawal preceded death in up to 90 percent of dying patients in critical care units[4-6] and 10 percent of admissions.[6] The proportion of patients dying with a decision to limit life support increased from 51 to 90 percent over the 5-year period from 1988[7] to 1992.[8] In Pediatric ICUs, retrospective studies in the last decade suggest that 40-60 percent of all deaths follow an end-of-life decision.[9] In contrast, in a tertiary care center in India; withholding and withdrawal of life-supporting interventions (WOLS) preceded only 22 percent of death[10] although in some other centers it is showing a signifícntly higher trend.[11] In the vast majority, however, the prevailing practice appears to be full, and often heroic, support until the very end.

The customary practices in India, however, may not accurately reflect the changing physician attitudes. In response to a questionnaire among 169 intensive care physicians in a recent survey 80 percent felt there is a need for forgoing life-supporting interventions in critical care and 55 percent practice "Do not resuscitate" (DNR) directives discreetly and unilaterally (Mani RK-personal communication). The majority appeared to have fears of misuse of the life- support limiting approach or of being misunderstood by the families of patients.

There are several impediments to change in end of life practices in India: The approach to the patient is generally "paternalistic", as the concept of autonomy is weak in the prevailing cultural ethos. The physician's orientation by his training is only to a curative approach to disease rather than to one of palliation when the patient's prognosis is poor. The physician is generally fearful of being accused of providing sub optimal care or of possible criminal liability of limiting therapies. Adding to his dilemma there is a virtual absence of ethical or legal guidelines relating to deaths in intensive care units. Self-determination of patients relating to medical decisions is not well articulated in our Constitution.[10] Indeed the position of the law with respect to death in dignity is unclear, as Indian courts have only addressed appeals for Euthanasia[12-14] In the US and in Europe the Laws have evolved over the last 3 decades to accommodate the changing paradigm,[15-17] while in India debate on the issue has only just begun.[18-20]

The need for change, however, is of vital importance for India for several reasons. There is an unbearable financial burden to the average patient as healthcare expenses are borne mostly by the individual. Lack of appropriate policies for limiting life support make fair distribution of scarce facilities impossible in this populous country. A technologically prolonged dying process takes away the serenity and dignity accorded to it by the established cultural traditions and beliefs.

Ethical Principles

Among the four cardinal ethical principles upon which the practice of critical care is grounded, respect for patient's autonomy has come to take precedence over the other three-namely, beneficence and non-maleficence and distributive justice.[3,5,15,16,21,22] Autonomy means the Right to self-determination, where the informed patient has a right to choose the manner of his treatment. To be autonomous the patient should be competent to make decisions and choices. In the event that he is incompetent to make choices, his wishes expressed in advance in the form of a Will, or the wishes of surrogates acting on his behalf "substituted judgment"[3] are to be respected.

Beneficence is acting in what is (or judged to be) in patient's interest. In critical care, increasingly the physician is expected to care for patients with a high risk of death. The principle of Beneficence requires that the physician act in the best interests of the patient and his family, and therefore, his responsibility should extend beyond medical treatment to ensuring compassionate care during the dying process. In this context, the physician's expanded goals include facilitating (neither hastening nor delaying) the natural dying process, avoiding or reducing the sufferings of the patient and his family, providing emotional support and protecting the family from financial ruin. **This is not to be confused with Euthanasia, which involves the direct intervention by the physician with the intention to hasten the dying process by administering a lethal injection or by other means.** When the physician, acting unilaterally, makes decisions for the patient, he is said to be "paternalistic".[15,16] Respect for patient's autonomy requires that Beneficence also consist of educating the patient to enable him to make an informed choice.

Non-maleficence means to do no harm, to impose no unnecessary or unacceptable burden upon the patient. This is subject to varied interpretation, as the same act may be construed as harmful or beneficial depending on the circumstances.[21] In practical terms, it requires the physician not to act contrary to the patient's values and perspectives.

Distributive justice means that patients in similar circumstances should receive similar care. Physicians need to have a socially responsible behavior, which makes it their duty to make good use of the material, financial and human resources under their control. The physician may thus provide treatment and resources to one with a potentially curable condition over another for whom treatment will be futile.[21]

When to initiate end-of-life (EOL) discussions:

A workable instrument of mortality prediction is necessary to identify situations where EOL discussions can begin. Whether a patient is going through the dying process or not is not always clear. Often the clinician's judgment is colored by his own biases and attitudes towards death.[24-26]

As with any diagnostic process identifying these situations needs expertise and experience. Each of the following criteria is not to be used in isolation, but in the context of the entire clinical history and status of the patient. When faced with prognostic uncertainty the physician should not take precipitous decisions but wait for the disease process to unfold.

The following list is not to be regarded as definition of medical futility, but should help the physician to recognize when to start discussions on EOL issues.

Checklist for initiating EOL discussions:

1. Advanced age coupled with a poor premorbid state due to chronic debilitating diseases. E.g., advanced chronic

obstructive pulmonary disease (COPD) requiring home oxygen and/or bilevel pressure support or with severe impairment of quality of life; advanced interstitial lung disease on oxygen therapy with failed medical treatment, chronic renal failure requiring long term dialysis, chronic liver disease, advanced congestive heart failure.

2. Catastrophic illnesses with organ dysfunctions unresponsive to a reasonable period of aggressive treatment.
3. Prolonged coma (in the absence of brain death) due to acute nonreversible causes or chronic vegetative state.
4. Incurable chronic severe neurological states rendering meaningful life unlikely e.g. Progressive dementia, quadriplegia with ventilator dependency.
5. Progressive metastatic cancer where treatment has failed or patient refuses treatment.
6. Postcardio respiratory arrest non-restoration of comprehension after a few days.
7. Comparable clinical situations coupled with a physician prediction of low probability of survival.
8. Patient/family preference to limit life support or refusal to accept life support.

Rationale: Absolute certainty in the anticipation of death is impossible. However, mortality prediction is central to communication and decisions in the critical care setting. A variety of scoring systems have been developed based on physiological variables, however, none is reliable enough to be adequate for individual patients.[23,27]

Despite these difficulties empirical data has accumulated that can guide the physician's predictive judgment. Indirect evidence for the validity of the "checklist" is found in the form of epidemiological data on ICU mortality and ICU use by decadents,[2] prospective and retrospective observational studies on WOLS[5,6,27,28] and from predictive tools that have been used in prospective studies on DNR and WOLS in both Emergency Room and ICU setting.[31,33] These data help to identify the patient characteristics that physicians generally use for limiting aggressive therapy.

In the US Angus et al[2] reported epidemiological data, which revealed that among infants most deaths occurred in hospitals, especially ICUs while above the age of 75yrs both ICU and hospital admissions at the time of death decreased, and beyond 85yrs, it was the least at 14 percent. ICU use was found to be limited for metastatic cancer as compared to acute myocardial infarction. These data clearly suggest that advanced age and certain disease conditions lead the physicians to limit ICU admission and aggressive treatments.

According to a multicenter, prospective, observational study in Europe, decisions for limitation were related to age and diagnosis among others.[6] Age, poor prognosis and poor quality of life were among the reasons cited in studies from France[5] and Canada.[28] In the latter series, the mean age of patients undergoing withdrawal of support was 65+/- 14.6, most of who had severe or extreme dysfunction of at least one organ system. They also found that the timing of WOLS decisions from ICU admission depends on the type and severity of the disease. These data again give us an insight into what considerations lead physicians to shift to palliative care.

Physician subjective estimates of intensive care survival < 10 percent are associated with a high probability of subsequent life support limitation and intensive care mortality,[27,29] but it is difficult to standardize.[30]

Evidence from DNR directives or ICU admission policies also helps to define how physicians may anticipate death with a view to initiating EOL discussions. Sinuff et al[31] found that physician prediction of low probability of survival, physician perception of patient preference to limit life support, medical rather than surgical diagnosis and age are the strongest independent determinants of DNR directives. An earlier study[32] did not find age or severity of illness as independent predictors for WOLS decisions, for the latter as compared to setting DNR directives are more complex requiring physician-family consensus. Similarly, Le Conte et al[33] reported the determinants of DNR directives to be advanced age (mean age 75+/−13 yrs), chronic cardiopulmonary disease, metastatic cancer or patients with acute non-treatable illness.

Recently,[34] it was found that having DNR and WOLS checklists improved the conduct of end-of-life care in the ICU as perceived by nurses.

In acute processes, response to therapy may often be surprisingly good and observations over time or serial scoring coupled with physician prediction may improve prognostication.[30] In the ETHICUS[6] study the greatest frequency of limitations occurred for acute neurological diseases.

For quadriplegics, the option of home ventilation should be offered along with the relevant information and counseling, but the choice of the patient or family should guide the decision.

It should be noted that "cut off" values for age or duration of observation before considering EOL care are hard to determine as they vary with the overall health status of the patient and the nature of his disease.

Absolute objectivity in mortality prediction has so far been elusive. The American Thoracic Society definition of futility is therefore suggestive rather than definitive: "A life-sustaining intervention is futile if reasoning and experience indicate that the intervention would be highly unlikely to result in a meaningful survival for that patient".[35]

For pediatric patients: Worldwide pediatricians are becoming more proactive in managing death and dying.[36] The EAC-RCPCH guidelines[37] cite the following situations as justification for limitation and withdrawal of interventions:

1. The permanent vegetative state
2. The "no chance" situation where there is expectation of imminent death despite aggressive treatment.
3. The "no purpose" situation where there is decrease in quality of life despite potentially extended survival.
4. The "unbearable" situation where in the face of progressive illness further treatment is more than can be borne.

GUIDELINES FOR LIMITING LIFE-SUPPORT INTERVENTIONS

Guideline 1

The physician has a duty to disclose to the capable patient or family, the patient's poor prognosis with honesty and clarity when further aggressive support appears non-beneficial. The physician should initiate discussions on the treatment options available including the option of no specific treatment.

Rationale: Respect for patient's autonomy and the imperative to act in his best interest are the basis for providing accurate information, as worldwide we move away from the "paternalistic" model of care.[6,15,22,23,35,38] It is important for the physician to identify a suitable family member as a surrogate decision- maker for the patient, as according to one study less than 5 percent of patients are able to communicate with the physician regarding issues relating to life support.[7,8,23] The "family" means spouse, children, parents, siblings, and the next of kin who is available or even a trusted friend, though a hierarchy of surrogates does not exist in Indian Law for making medical decisions. Advance Directive stating the patient's preference is not a practice in India but public awareness in this regard should be encouraged.

Curative and palliative measures are coexistent but varying in degree at different phases of critical illness.[17,38] Therefore, the physician must initiate discussions early with a clear expression of the patient's condition. Waiting, watching and postponing discussions on prognosis may be more stressful to the family as well as the ICU staff.[39]

Practice points:

a. It is important that the physician gives as accurate a prognosis as is possible, clarifying that uncertainty is inherent in the treatment of critical illness, in a language and in terms that the family can understand.
b. It is the responsibility of the physician to inform the capable patient or his family the diagnosis, prognosis, the range of appropriate therapeutic interventions available as well as the option of no therapy, including their risks, benefits, costs and consequences.[35]

Guideline 2

When the fully informed capable patient or family desires to consider palliative care, the physician should offer the available modalities of limiting life-prolonging interventions.

If the patient or family do not desire the continuation of life supporting interventions the available options for the use of life-sustaining supports should be identified as follows:

1. Full support
2. Do not intubate (DNI) or Do not resuscitate (DNR) status
3. Withholding of life support
4. Withdrawal of life support
5. Palliative care

Definitions: Modified[4]

Full support: All measures needed to to support hemodynamics, metabolism and ventilation.

Full resuscitation (CPR): Aggressive ICU management up to and including resuscitative attempts, in the event that cardio respiratory arrest occurs.

Do not intubate/resuscitate (DNI/DNR): Aggressive ICU management up to, but not including endotracheal intubation (DNI) or attempts at CPR (DNR).

Withholding of life support: The considered decision not to institute new treatment or escalate existing treatments for life support (intubation, inotropes, vasopressors, mechanical ventilation, dialysis, antibiotics, intravenous fluids, enteral or parenteral nutrition) with the understanding that the treatment has a higher potential to cause pain and suffering than resolution of organ failure.

Withdrawal of life support: The cessation and removal of an ongoing life supporting treatment while not substituting an equivalent alternative treatment, with the understanding that the treatment in question is causing pain and suffering and serves no purpose other than delaying death. It is fully anticipated that the patient will die following the change in therapy primarily because of the underlying disease conditions.

Palliative care: No further attempt at resuscitation or providing hemodynamic or ventilatory support. Active measures aimed at only alleviating pain and suffering when the disease process has reached a point of no return.

The committee of the Indian Society of Critical Care Medicine emphasizes that Euthanasia and Physician Assisted Suicide are illegal in India and should not be practiced.

Euthanasia is allowed in the Netherlands under certain strict regulations. Physician-assisted suicide (PAS) is legal only in the State of Oregon in the US. In India, the Supreme Court does not recognize that a terminally ill patient has the Right to choose the manner of his death.[40] Requests for Euthanasia have been turned down,[12,13,14] and suicide and abetment to suicide are declared punishable by the Indian Penal Code.[10]

The other definitions are:

Physician assisted suicide: A medical doctor provides patients with means to kill themselves.

Euthanasia: The intentional killing of a patient by the direct intervention of a doctor, ostensibly for the good of the patient or others.

Brain death: Irreversible cessation of all functions of the brain including the brainstem. In the US, brain death is death. This category does not include patients who maintain brainstem function, such as patients with persistent vegetative state.

In India, brain death is defined only for the purpose of the Transplantation of Human Organ Act 1994. Indian law does not define the state of brain death in contexts other than organ transplantation. In the opinion of the Committee, brain death should be regarded, as equivalent of death in all circumstances and the law should be suitably amended.

Guideline 3

The physician must discuss the implications of forgoing aggressive interventions through formal conferences with the capable patient or family, and work towards a shared decision-making process. Thus, he accepts patient's autonomy in making an informed choice of therapy, while fulfilling his/her obligation to provide beneficent care.

Rationale: Communication with the family is the key to making appropriate decisions and ensuring quality end-of-life care in the ICU.[17,23,38,41-47] If the best interests of the patient and family are to be served, they should be involved in an informed decision-making process at the outset. Surrogates need to be well informed and free from incapacitating anxiety and depression to be able to function effectively as substitute decision-makers for the patients.

Early and effective communication facilitates a more smooth transition from curative to palliative care, reduces the frequency of futile care and decreases the possibility of conflict and litigation between families and health care workers.[38,41,47]

The correlates of effective communication and family satisfaction include the provision of adequate time, frequent and consistent information provided by a single contact physician, preferably an intensivist, adequacy of physician and nurse staffing and help from the family physician are also beneficial.[41,42,43] Ensuring enough time for the family to ask questions and express themselves further enhances family satisfaction.[38]

Practice points: Empirical evidence from other cultures may not be applicable in India, where the impact of socio-cultural influences upon family needs have not been studied. We can however integrate the generalizable points into ICU practice in India:

a. The discussions should be between the family and an intensivist. The presence of a nurse and a junior doctor will ensure consistency in subsequent discussions. It is desirable for the primary consultant and/or the family physician to be present.
b. There should be multiple counseling sessions of adequate duration. Family must be given adequate time and opportunity to ask questions and to express their views and emotions. This should be done in a manner that ensures privacy, in a waiting room or similar area.[44]
c. The possibility of death should be discussed along with the medical and palliative treatment options. The intensivist should enquire into any previously stated terminal care wishes or preferences directly or indirectly expressed by the patient. The discussions should include the relevant economic, ethical and legal issues.
d. The family members may express feelings of guilt or remorse that should be resolved with patience. It might be useful to remind the family that death is inevitable and medical science cannot offer cure in all situations; that during the dying process the patient needs a humanistic approach rather than a purely technical one. In case the family has difficulties in accepting the possibility of death counseling by a professional psychologist may be considered.

Guideline 4

Pending consensus decisions or in the event of conflicts between the physician's recommendations and the family's wishes, all existing supportive interventions should continue. The physician however, is not morally obliged to institute new therapies against his/her better clinical judgment.

Rationale: The physician should not unduly influence the family in decision-making.[7,23,35] Though the emphasis on patient autonomy versus medical paternalism varies in different countries and societies,[3,5,16,23] the worldwide trend is towards a shared decision model.[3,22,23] This would minimize the influence of physician preferences, social and religious biases on the issue of forgoing life support.

Several professional recommendations support the view that the physician may not be pressurized to apply treatments he does not find appropriate.[23]

Practice points:

a. The physician should guard against imposing his own values on end of life decisions or be in any way manipulative or coercive.
b. Decision may be taken in a stepwise manner towards de-escalating the treatment through discussions until the picture becomes clearer to the family.
c. Conflicts may be resolved through improved communication and deferring decisions until the family is able to come to terms with the realities of the patient's condition. Second opinions or a psychologist's consultation may be sought. A social worker, a religious guru or a respected family elder could help overcome barriers to understanding.
d. The physician may not subject a patient to a particular therapy, even if the family may demand it, if it is against his professional judgment.

Guideline 5

The discussions leading up to the decision to withhold life-sustaining therapies should be clearly documented in the case records, to ensure transparency and to avoid future misunderstandings. Such documentation should mention the persons who participated in the decision-making process and the treatments withheld or withdrawn.

Rationale: Documentation implies transparency, clarity and evidence of an evolving decision-making process that indicates appropriate care on the part of the physician. This would be helpful to the physician to demonstrate his bonafide intentions in the event of litigation. It would provide security for the patient in case of malafide intentions on the part of caregivers or his own family. It would also ensure that the patient is informed of all the therapeutic choices available and that overall management plans are spelt out for him. Clear documentation is strongly recommended by European professional societies[23] and the American Thoracic Society.[35]

Practice point: Details of the communications between the medical team and the family should be documented accurately and completely. The Committee does not regard the signature of a family representative to be a mandatory requirement. The specific modalities withheld or withdrawn should be documented.

Guideline 6

The overall responsibility for the decision rests with the attending physician /intensivist of the patient, who must ensure that all members of the caregiver team including the medical and nursing staff agree with and follow the same approach to the care of the patient.

Rationale: The physician in charge of the patient is ultimately responsible for the decision although the process of decision-making requires full participation by the family/patient. The burden of the decision should not be put upon the family as several studies have found surrogates wanting in decision-making capabilities for the patient.[48,49,50] The leadership role assumed by an intensivist with his experience and expertise generates trust and confidence in the family.[23] Physicians/intensivists should minimize inconsistencies between members of the treating team.[41]

Practice point: Medical decisions and prescriptions should be made by the primary physician/intensivist. This should take into consideration and integrate the opinions of the various sub-specialists involved in the patient's care. The primary physician/intensivist should ensure communication and uniformity between the various members of the healthcare team.

Guideline 7

If the capable patient or family consistently desires that life support be withdrawn, in situations in which the physician considers aggressive treatment non-beneficial, the treating team is ethically bound to consider withdrawal within the limits of existing laws.

Rationale: Physician's obligation to respect patient's autonomy and to act in the patient's best interests does not permit him to continue a futile treatment even though the legal position is unclear. In the absence of case law, the physician may be apprehensive of the potential for litigation in the future. Obtaining signed consent for withdrawal of support may be viewed as protective to the physician but as coercive to the family. The process of withdrawal must find a suitable balance between the two concerns.

Practice points:

a. Since Indian Law has no clear stand on end-of-life issues except that suicide and abetment to suicide are punishable offences,[10] withdrawal even with the expressed consent of the patient or next of kin can be misinterpreted *post hoc.*
b. The physician must ensure clear documentation of the detailed discussions with members of the family who should be specified. The concerned physician, family member or both may then sign the records.
c. Terminal care may be offered in the ICU, or in another area of the hospital in keeping with the wishes of the family. If the patient is discharged from the hospital preterminally, an appropriate discharge process ("discharged on request", "left against medical advice" or "discharged against medical advice"), in keeping with the hospital policy, should be followed.

Guideline 8

In the event of withdrawal or withholding of support, it is the physician's obligation to provide compassionate and effective palliative care to the patient as well as attend to the emotional needs of the family.

Rationale: The US Supreme Court implicitly endorses the practice of using analgesics and sedatives to ensure that no patient dies in pain or distress.[38] However, in high doses side effects may take place that may hasten the dying process. Physician-assisted suicide needs to be distinguished from these as hastening of death is unintended, the primary goal of therapy being only alleviation of pain, dyspnoea, or distress. Quill and associates termed it "the double effect" to distinguish the intended and unforeseen effects.[51] Since the Court cannot recognize intentions, we should take care to document the use of opiates and the indication for their use.[15] This reduces the likelihood of misinterpretation or abuse.[15,38]

Practice points: When patient undergoes withdrawal/withholding of life-sustaining modalities, the physician is ethically obliged to continue to provide care that would alleviate the patient's distress:

a. All ethical issues relating to withdrawal should be discussed thoroughly with the family.
b. If the patient is conscious and *compos mentis,* he should be clearly and with sensitivity explained what is expected to happen when a support is withdrawn. He should be reassured that possible pain or distress will be prevented by medication and prompt action should be taken for symptom relief.
c. The optimal dose of opiates is determined by increasing the dose until the patient's comfort is ensured. There is no maximum dose recommended.[17]
d. The physician should continue to be available to the family for guidance and discussion.
e. For patients discharged home for terminal care suitable arrangements for transport and home care should be made.
f. The patient's family should be allowed free access to the patient during the last days of his life.[42,43] In this situation, it would be permissible to allow children to visit the patient. The family should be encouraged to participate in the general care and nursing of the patient.[38] Music, books, TV etc. that can help alter the environment should be made available. The patient should be allowed every

opportunity to experience spiritual meaning and fulfillment. Performance of non-obtrusive bedside religious services or rites should be encouraged.

Medical Futility and Unilateral Decisions by Physicians

There are situations when the patient's family may insist on continuing life-support despite hopeless prognosis. The physician may have to act against his better judgment and thus face loss of self- esteem and professional integrity. Even in cases of documented brain death, there have been occasions when supports have had to be continued due to surrogates' unreasonable stand that everything possible should be done. We are obliged to define these situations and seek legal instruments to implement unilateral withdrawal of support.

What Constitutes Medical Futility?

Here we are referring to clinical situations where in the absence of brain death the physician believes that continuing life support is futile and may justifiably take a unilateral decision to limit life- supporting interventions for the patient. Clear and unequivocal situations of medical futility are rare. Futility may be "quantitative"(how low are the odds of success) or "qualitative" (what are the desired ends).[52] There is no consensus among physicians about the exact definition of futility. More often than not, the issue is conflict resolution.[35] There may be misunderstandings regarding prognosis, the family may be pursuing unrealistic and unwanted plans, or the physician may be seeking to impose his ideas on the family. Examples of situations where the physician may consider unilateral action are: patient has a prognosis of imminent death; patients with metastatic cancers in whom treatment has failed or has been declined; the very elderly with dementia; chronic vegetative state with organ dysfunction.

The proposed course of action may be:

1. A second opinion from another physician not hitherto involved in the care of the patient.
2. Multiple counseling sessions with the family explicitly informing the family the hopeless prognosis of the patient and the futility of continuing life support.
3. If the family is intransigent, then suggesting transfer to another treating team willing to continue supports.
4. With the help of the hospital administration, to set up a committee of doctors to counsel the family. The committee may also take the help of a social worker, psychologist or priest to help resolve barriers to understanding.

Seeking a judicial review of medical cases for WOLS decisions has no precedence in India. Therefore, from the legal perspective unilateral action is not available to the Indian physician at present.

CONCLUSIONS

Setting goals appropriate to clinical situations of poor prognosis are an integral part of critical care. Quality critical care requires that the practice be well grounded in ethical principles and that the ICU staff is trained in the skills of end of life care. A consensus regarding the practices relating to end-of life care in Indian ICUs should eventually lead to the evolution of appropriate legislation in keeping with the changing needs of critical care practice.

Disclaimer: This is the executive summary of the guidelines developed by the ISCCM Committee and represents the ethical position of the Indian Society of Critical Care Medicine. The guidelines are designed to provide a path to ethical decision-making. This document is not intended to provide legal advice on related issues in individual cases where physicians should seek appropriate legal guidance.

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CHAPTER

Psychological Issues in PICU

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Implications of admitting one's child in a hospital can be far reaching. It affects every day routines, hopes and ambitions and relationships both between family members and with outside world. Parents of children who have been diagnosed with a particular condition are often confronted with a medical context that is unfamiliar to them.[1] To receive a diagnosis does not always imply that parents receive information about the aetiology of the condition or about its consequences for the child.[2] This means that parents could be left without professional support and with unanswered questions concerning their child's condition.[3]

CHILD'S REACTION TO HOSPITALIZATION

Before understanding the sources of stress during hospitalization it is important to understand the impact of illness and hospitalization on children and their caregivers. There are several domains and perspectives through which one can understand the impact of illness and hospitalization. The developmental biopsychosocial model proposed by George Engel is one model that takes all the perspectives into account.[4] The developmental biopsychosocial approach addresses the complexity of interactions between different domains of functioning and argues that it is the interaction of domains that illuminate important processes.It stresses that all medical phenomena, such as a child's reaction to illness, hospitalization and surgery, can best be conceptualized through a thorough understanding of developmental, biological, psychological, and social information concerning all the key persons involved. The model proposes that a true understanding of complexity of health and disease can only be achieved by considering the ongoing interplay of these four sets of information.

Developmental Sphere

The focus is primarily on the developmental level of the child. The main question to ask in the developmental category is: "What is the current, premorbid developmental stage and functional level of the child?" There are several responses to illness and hospitalization such as anxiety, regression, mood changes, and changes in bodily functions (e.g., eating, sleeping) that are typical of persons of all ages but these responses are characteristic of an individual developmental level. Different-age children, depending on their developmental level, have different key concerns or tasks that influence how they perceive all events. Thus, their understanding of illness and hospitalization also differs, depending on their developmental level which is explained in more detail below:

1. Children age 3 years and under are establishing primary attachments. They are learning to regulate attention and other body functions. While they have access to opportunities for exploration and learning, their caregivers protect them from pain and overwhelming stimuli. Children in this age range have little concept of illness. They view it as an external agent that causes discomfort and pain. They depend almost totally on their external caregivers to relieve them of what bothers them.

2. Children 3 to 7 years old are typically concerned with abandonment, punishment and bodily harm. They have begun separating and individuating from their caregivers on whom they still remain largely dependent. These children are better able to understand illness as something going on inside themselves, yet often they have unique ideas to explain why they are sick, including the concrete interpretation that the illness is a punishment for real or perceived indiscretions by the child.
3. Children between the ages of 7 and 13 years are working to master fears of loss of control and fears of death. These children have a greater understanding of illness and themselves, but they still believe that they have done something wrong or that they acquired the illness through contagion. Children at this age can be told more about their illnesses and can be more actively involved in their treatments.
4. Teenagers between 13 and 18 years are primarily concerned with their physical appearance, self-image, real or potential loss of peers, and fears of dependency. Adolescents understand their illnesses in ways approaching those of mature adults. They can test hypotheses logically and entertain numerous causes for their condition. They depend less on their caregivers, are more able to care for themselves, and generally prefer the company of their peers. Under stress, however, they still tend to consider illness to be a punishment for some indiscretion only known to them.[5]

It is important to take individual differences into account. Changes in both developmental tasks and cognitive abilities vary among children of similar ages and can differ from individual to individual. It is important for health professionals to understand developmental concepts enough to ask how the illness is affecting the child and be sophisticated enough to listen and respond to concerns or inexact theories that reflect developmentally based misperceptions.

Biological Sphere

The emphasis in biological sphere is mainly aimed at determining the biological and organic correlates of the suspected problem. This entails investigating the constitutional strengths and weaknesses of each patient, including their genetic endowment, response to medication, biological manifestations of the illness, perceptual skills, learning capabilities, ability to attach and maintain relationships, temperament and predisposition to mental illness.

Psychological Sphere

The primary focus is aimed at understanding how a child think about and react to his or her illness. Individuals actions are based on the perceptions they have and these perceptions are based on their past experiences. Thus it is important to understand and elicit the child's perception of the illness. This again should consider the developmental aspect related to the child.

EFFECTS OF HOSPITALIZATION ON THE FAMILY OF THE CHILD

Social Sphere

The main aim in this sphere is to understand as to how the family and other caregivers (including the medical team) are dealing with the ill child. The main questions in the social category are aimed at understanding the strengths and weaknesses of the caretaking environment including individual, cultural, societal and national values. In keeping with the developmental biopsychosocial approach, each family member and caregiver is considered to be a separate, yet interrelated entity with its own developmental, biological, psychological and social issues.

It is important to understand that the patient as a unit of a family has the power to contribute to the onset of physical or psychological dysfunction in one or several family members- and to the disintegration of the family as a unit. By the same token family has the power to adversely influence the patient's capacity to adapt to his illness. Thus in order to understand the impact of illness on children it is important to understand the impact of illness on the family members or the caregivers.[6] Thus it is important to assess the caregivers reaction to illness and hospitalization by looking at the developmental, psychological, social and biological aspects.

Developmental Dimension

It is important to understand where are the caregivers developmentally? There are individual differences in the coping abilities of adults. Many adults have limited ability to abstract and understand therefore it becomes important to assess the caregivers on this dimension.

Biological Dimension

There are several areas in this sphere which can be looked upon. One such area is to determine the innate intelligence of the primary caregiver. Occasionally caregivers are so compromised in this area that special intervention programs are needed. It is important to understand the temperament or personality of the caregiver. Temperament and personality act as a filter through which medical information, decision-making, and communication flows. In this sphere it is also important to know whether stress has triggered any specific mental disorder in caregiver or not.

Psychological Dimension

These questions are aimed at understanding how the illness fits into and changes the story, or narrative, of the caregiver's life. How psychologically minded are the caregivers? Can they understand that the illness is a stress for themselves and other persons involved? Most importantly, can they empathize with the plight of their sick child and appreciate the child's needs? It is equally necessary to understand as to how caregivers deal with the stress?

How do the caregivers deal with stress? What coping and defense mechanisms do they use (denial, rationalization, intellectualization)? It is important to adopt and use healthy ways of coping associated with a particular stressful condition. Unhealthy coping patterns may further complicate the condition and lead to more stress.

What is the impact of past or concurrent illnesses on the caregivers and what are the caregiver's past experiences with health care providers and systems? It is important to consider the past experiences because on these experiences human perception is formed. A bad experience in the past can create anticipatory anxiety, complicate relationships with the health care team, and further complicate treatment.

Social Dimension

The social sphere addresses the support system of the caregiver. It is important to have a good support system in order to deal with a stressful circumstance. Healthy relationships with one friend, family and other people help one to adjust and deal with a stressful situation. One must also consider the religion as it plays a pivotal role in the way many families deal with illness. Religion can provide an understanding of the event and place it in a larger spiritual context that may or may not prove helpful. Various religions provide different explanations of the place of illness in life. Because of this, it is important to know the tenets of a family's religion. However, persons interpret religious doctrine in ways that reflect their own personality and past experiences. These variances can greatly influence the course of the illness and its treatment.

Thus looking at all these dimensions will provide a complete understanding of the complexity of interactions between different domains of human functioning.

SOURCES OF STRESS IN A HOSPITAL SETTING

Staying in a hospital can be extremely depressing and stressful both for parents as well as the child. Hospital admission creates a number of stresses for the child such as stress of separation from parents, the pain of treatment, the unfamiliarity of the environment, and the fear of unknown.[7] Some of the difficulties experienced by the parents may stem from the unfamiliarity of the hospital setting. Other difficulties may derive from the way in which hospitals in particular are organized for example- In India, in a government setting, it is difficult to communicate effectively and adequately to every patient and his/her family members as the number of patients seeking medical care is very high. In a private set up on the other hand, efforts are made to communicate effectively to every patient and his/her family members about the medical condition and other complications associated with it.

Some of the common sources of stress for parents include:

Unfamiliar Hospital Environment

One of the problems of staying in a hospital setting is unfamiliarity with the hospital setting, where it is difficult to know the way around, who does what, where and when to ask for information, how and when things happen, what to or what is expected of oneself.[8]

Losing the Parental Role

Child's physical, psychological, social and spiritual needs are met primarily by the family. Hospitalization of a child not only affects the nature of some or all of these needs but also the ability of the family to meet them. Hospitalization of a child forces changes in the parents' view of themselves as protectors and nurturers. They may have to relinquish much of their parenting role to the nurses.[9]

Costs of Staying in a Hospital

Cost of staying in a hospital may spread over different dimensions including economic, social and personal.

1. *Economic*—This may include all the expenses involved in the treatment such as costs of traveling to hospital, buying meals, medicines and telephones. Apart from it staying in a hospital with a child also results in loss of income especially when parents are self-employed.
2. *Social*—Admitting one's child in a hospital may isolate the parents from their usual resources, social roles and social networks.
3. *Personal*—Participation in all the unpleasant experiences such as seeing one's child in pain may result in guilt and apprehension in parents because it challenges parents' ideas of themselves and their usual roles in providing for or protecting their children.[10]

Physical Health of the Child

For all parents of children with serious illness, one of the most important sources of stress will be anxiety about the child itself and his or her physical condition. A number of studies have been undertaken to explore these problems at particularly critical junctures:

The degree of stress and anxiety in parents may vary according to the physical condition of the child.

1. Unexpected and Sudden Admission

An unexpected admission in a hospital may result in greater anxiety and stress. In a study it was found that mothers, whose children had been admitted unexpectedly to a pediatric intensive care unit, reported catastrophic feelings of shock, guilt, helplessness and confusion.[11] Other important findings that emerged from the study found that parents experienced a lot of tension while waiting for their partners to reach the hospital. Other sources of stress was waiting in acute stress without nursing assessment or therapeutic support through a period of enforced separation during the medical stabilisation of the child and being re-united with a child whose appearance had changed (being nursed naked, incubated, ventilated and attached to a variety of monitors and infusion devices).

2. Treatment Complications

In some cases it is not possible to completely cure the illness. In such cases, some unavoidable damages may occur to the child. A study of the experiences of parents whose children suffered neurological damage after cardiac surgery[12] found feelings of shock, loss and grief, combined with a profound sense of "aloneness". Parents also reported feelings of guilt, blame and anger - almost all the parents identified a specific focus of blame for their child's brain damage. These included "medicine", "the child" and "themselves".

3. Dying Child

In order to comprehend the impact of an impending loss and the human behavior associated with it, it is important to have some understanding of the meaning of the attachment. There is considerable work done by John Bowlby to understand the nature of attachment. Human beings have a tendency to make strong affectional bonds with others.[13] These attachments come from a need for security and safety, they develop early in life, are usually directed toward a few specific individuals, and tend to endure throughout large part of the life cycle. The situations that endanger this bond give rise to certain very specific reactions.[14] The death of a child has been repeatedly identified as the most traumatic experience a family will endure.

ROLE OF NURSE IN HELPING CHILD AND FAMILY IN COPING WITH STRESS OF HOSPITALIZATION AND ILLNESS

The entire process of coming into a hospital is a new and demanding experience. An experience which requires a lot of adjustment both from the caregivers and the child. In order to understand the impact of illness and hospitalization on children and their caregivers it is important to understand and incorporate the developmental, biological, psychological, and social aspects. Nursing has an important role to play in facilitating communication, with compassionate and caring attitude to minimize the associated stress. Taking all these dimensions together will help one to understand the processes associated with human functioning. Some of the common sources of stress in a hospital are unfamiliar hospital setting, restriction in one's movement, losing one's parental role, economic, personal and social worries. The amount of stress experienced by the caregivers may also vary according to the physical condition of the child. If the child is critical and about to die then the amount of stress experienced by the parents would be more as compared to a child who may get well in few days. It is important to understand the manifestations of grief and bereavement at this point. Most parents are able to cope with their feelings of loss but some have trouble resolving their feelings about the loss. It is necessary to understand the needs of the grieving parents and develop some effective strategies to deal with it. The main focus of these strategies should be to provide assurance, hope and support in order to deal with the anxiety, stress and discomfort experienced. If the parents are facing trouble in resuming a normal life then seeking psychological help from a mental health professional is required.

CONCLUSION

Admitting one's child in a hospital alters the way of life experienced by the child as well as the family. There is no doubt that parents need assurance, support and psychological help during their stay in a hospital. Nursing has a key role to play in minimizing the stress of the sick child and the family by being supportive and reassuring at all times.It is important to understand all the sources of stress associated with patients stay in the PICU. For a holistic understanding it is seminal to incorporate the perspectives of both the health care professionals as well as the caregivers.

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Section Eleven

Environmental Injuries

CHAPTER

96

Thermal Burns

RK Seth, Praveen Khilnani

The most important early discussion of burns in the English Language was by John Kentish, who in 1797 published a monograph entitled "An essay on Burns". In this essay he advocated exposure therapy in the early stages of the burns, but later he preferred the use of occlusive dressings. James Earle (1799), in a series of publications which appeared at about the same time, discussed many aspects of burn treatment of initial pain. Few changes were made in therapy throughout the nineteenth century, except for the use of the continuous both. The first modern discussion of burn therapy was published by Sneve (1905) in a remarkable article entitled "The Treatment of Burns and Skin Grafting". Between 1909 and 1915 reports on the open air treatment of burns appeared under the authorship of Neathery (1909), St. John (1910), Hermann (1915), and Hass (1915). In 1941 the era of antibiotic topical agents was introduced with the preliminary reports on the topical use of sulfanilamide. Since 1950, the increased understanding of fluid and electrolyte therapy, improved methods of combating shock, and better understanding of the metabolic, nutritional, hematologic and psychologic aspect of burn care have been recognized.

Pediatric thermal burn management is presented in the following chapter with emphasis on two areas:

1. Standardization of intensive care management of a child with lesions involving 20 to 80 percent of the body surface area.
2. Treatment of complications due to loss of critical amounts of skin, unusual depth of burn, involvement of critical areas such as the hands, face, eyes, respiratory tract injury, fluid and electrolyte abnormalities, concomitant disease or trauma and infection.

Certainly, over the past 45 years, with establishment of burn centers, patients with major pediatric burns have received a rapidly evolving special attention by team of emergency physicians, plastic surgeons, pediatric intensivists, nutritionist, physiotherapist and rehabilitation specialists to achieve the improved survival statistics as well as reduced long-term morbidity.

Etiology

The cause of burns varies from one part of the world to another, depending upon local customs with respect to the use of fire. Burns occur frequently in India because of the small, open cooking stoves in common use, spillage of hot liquids in the kitchen; molten metal burns occurs frequently in certain specialized industrial areas. Of the total number of burns which require hospitalization approximately 50 percent occur in the home. Of these home accidents, atleast two-thirds are preventable.

Frequent causes of burns are:

1. Flame and flash burns
2. Scalds
3. Contact burns
4. Electrical burns
5. Chemical burns.

Classification and Diagnosis

Although the diagnosis does not pose a problem, the evaluation of the magnitude of injury is more difficult. "Extent of body surface burnt": An approximation of surface area involvement can be rapidly made by the "Rule of Nine". In children, a relatively greater amount is allowed for the head and trunk, and less for the lower extremities. For more accurate determination, a body surface chart as illustrated is preferred (Figs 96.1A and B).

Depth of Burn

The depth of the burn is largely dependant upon the temperature of the burning agent and the duration of contact.

The terms superficial, partial thickness and full thickness are preferable to first, second and third degree.

Partial thickness burns are further classified as:

a. Superficial partial thickness and
b. Deep partial thickness burns indicating the extent of dermal involvement (Table 96.1).

Determination of depth of the burn at the time of initial examination often difficult. The wound will vary in appearance but during the first few days, it is usually possible to ascertain if the wound is predominantly partial thickness or full thickness. In some instances, however, the most experienced with accuracy the exact depth of burn, and the true depth becomes apparent with the passage of time.

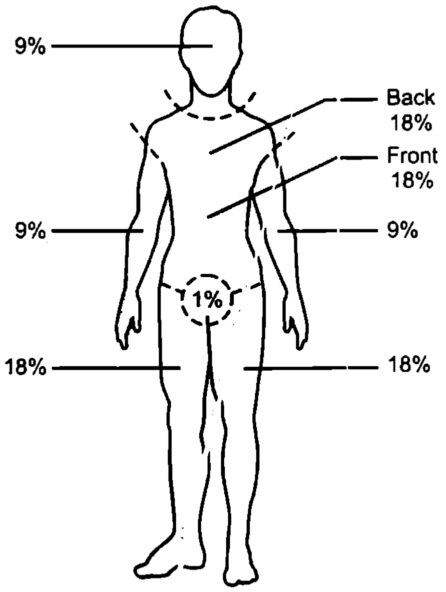

Fig. 96.1A: An estimate of the percentage of total body surface skin that is burned can be obtained by use of the "rule of nines," whereby the total surface area of skin is divided into areas equaling 9% of the total *(From Demling RH. Fluid and electrolyte management. Crit Care Clin 1985;1:34)*

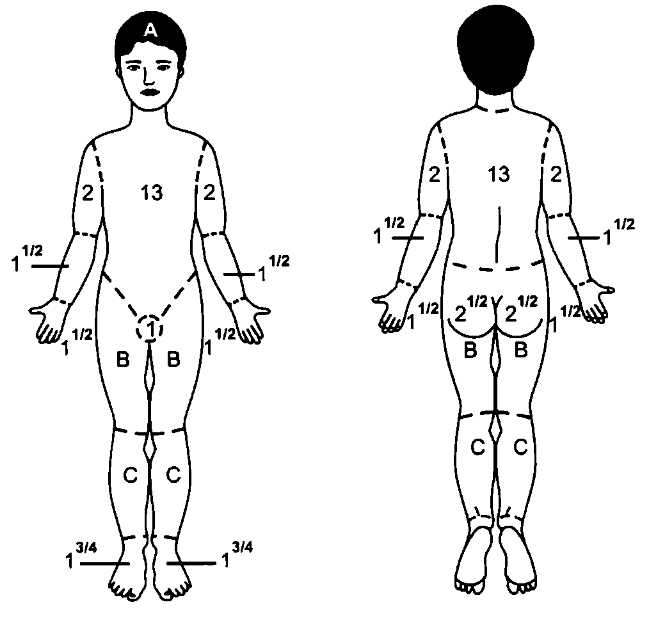

Fig. 96.1B: This chart of body areas, together with the table showing the percentage of surface area of the head and legs at various ages, can be used to estimate the surface area burned in a child *(From Solomon JR. Pediatric burns. Crit Care Clin 1985;1:161)*

Age of the Patient and Burn Injury

The age of the patient is an important factor in estimating the severity of injury. Burns are tolerated extremely poorly by extremes of age. Mortality rate in infants under the age of 12 months and in individuals past the age of 65 years is quite high, even in the presence of limited burns. In general, the mortality rate is low for individuals under the age of 50 who sustain burns of 30 percent of the body surface area or less. As the extent of burns increases beyond 30 percent, the mortality rate rises in all age groups.

Associated Injury or Concurrent Disease

In addition to the extent and depth of the burn and age of the patients, other factors involved in deter-

Table 96.1: Burn depth categories

Burn degree	*Cause*	*Surface appearance*	*Color*	*Pain level*
(First) superficial	Flash, flame, ultraviolet	Dry, no blisters, minimal oedema	Erythematous	Painful
(Second) partial thickness	Contact with hot liquids or solids, flash flame to clothing, direct flame, chemical	Moist blebs, blisters	Mottled white, pink, cherry red	Very Painful
(Third) full thickness	Contact with hot liquids or solids, flame, chemical, electrical	Dry with leathery eschar, charred vessels visible under eschar	Mixed white, waxy, dark, pearly, charred	Little or no pain, hair pulls out easily
(Fourth) involves underlying structures	Prolonged contact with flame electrical	Same as third degree exposed bone, muscle or tendon	Same as third degree	Same as third degree

mining the severity of the injury include any fractures or associated injuries sustained at the time of burning. It is becoming more common to see burn patients involved in automobile accidents in which associated injuries are quite frequent. *Smoke inhalation injury leading to pulmonary involvement as well as carbon monoxide poisoning* are important complicating factors. Facial burns lead to severe edema of the face as well as the airway within 48 hours therefore making elective intubation or early tracheostomy as mandatory procedures to protect the airway.

Any illness that the patient had prior to the time of burning may complicate an otherwise smaller burn. For example, patients with pre-existing renal or cardiovascular disease tolerate burning poorly.

Pathophysiology

Although there is a tendency for the uninformed to consider burn as a superficial skin problem, *the stress associated with the burn injury* is severe and can involve virtually every organ system in the body. The most striding immediate systemic effects following burning are related to the hemodynamic changes that occur. There is altered capillary permeability, so that water, sodium, chloride and proteins escape from the vascular compartments into the burn wounds. This creates the "obligatory" burn edema, which is characterized by extensive swelling about the face and neck following burns in this area.

As a result of excessive fluid, electrolyte and protein shift in burn edema, there is resulting hypovolemia and haemoconcentration, conditions which require intensive fluid replacement therapy.

Extravasation of fluid into the burn wound continues for 24 to 48 hours, the shift in fluid is due to 1) the stress mechanism, especially the elaboration of the mineralocorticoids, which result in retention of sodium, chloride, water and excretion of potassium; which allows egress of electrolytes and protein from the vascular compartment; and a capillary leak folllowing the release of inflammatory mediators such as cytokines, interleukins secondary to thermal injury.

Salt is lost from the vascular system in relatively greater amounts than water; water in relatively greater amounts than protein; albumin in relatively greater amounts than globulin fraction; and plasma in relatively greater than red cell mass.

Management

Immediate Emergency Care

A well-organised and coordinated approach is essential to assure that all required treatment is administered in an orderly fashion and in a proper sequence in the emergency room and the pediatric intensive care unit isolation area. The following is a workable guide for immediate treatment for burn patients:

1. *A quick general evaluation of the patient.*
2. *Establishment and maintenance of an adequate airway and breathing.*
3. *Fluid replacement therapy to combat shock.*
4. *Emergency sedation and analgesia if required.*
5. *Insertion of indwelling catheters early.*
6. *Tetanus prophylaxis.*
7. *Initiation of burn wound care.*

8. *Evaluation of antibiotic therapy.*
9. *Nutritional requirements and general supportive measures.*

General Evaluation

Fluid replacement, after making a rapid preliminary evaluation of the airway and breathing, should be initiated prior to recording of a detailed history and physical examination. Clothing should be inspected for estimation of the extent and depth of burn injury.

Establishment and Maintenance of Airway

The oral and nasal mucous membranes must be inspected for evidence of injury, such as hyperemia, and direct burning effect, such as singeing of the nasal hair and presence of soot and particulate matter. Relatively minor initial physical findings may herald the onset of serious pulmonary complications. One should not hesitate in inserting an endotracheal tube if transient respiratory difficulty is anticipated, especially with burns involving face and neck. In children, the level sedation and analgesia required with endotracheal intubation and burn pain management necessitates short periods of mechanical ventilation.

Endotracheal intubation may be tricky in patients with airway injury or extensive facial burns and a fiberoptic bronchoscope assisted intubation may be required under anesthesia. A stand by emergency tracheostomy should be arranged should intubation attempts fail. Laryngeal mask airway should be used in emergency if intubation failure occurs.

Patients with airway injury, and severe burns are susceptible to developing pulmonary edema and acute respiratory distress syndrome, will therefore need to be mechanically ventilated. Older children benefit from a humidified oxygen for the first 48 to 72 hrs via T-piece connected to the endotracheal tube if facial burns are significant. *A hyperkalemic response to depolarising agents such as succinyl choline may be seen resulting in ventricular fibrillation, specially 5 to 15 days post-burn period lasting 3 to 16 months.* Resistance to non-depolarizing muscle relaxants has been observed in burn patients, requiring higher dosing in mechanically ventilated patients.

Estimation of Fluid Requirement

Experience with large number of burn patients has resulted in the development of *several formulae for burn fluid replacement* (Table 96.2). It must be emphasized that all fluid replacement formulas are for the purpose of preliminary planning to estimate the patients fluid requirement. The subsequent clinical course including urinary output, response to initial therapy and onset of complications, will determine the amount and type of subsequent fluids, which must be administered.

Fluid requirement for burns of more than 50 percent BSA (body surface area) should never exceed that calculated for 50 percent BSA burns.

Brooke Army modification of the Evans formula and Parkland Hospital formula have proved to be quite workable as a guide for initial fluid estimates.

Fluid Replacement Therapy

As a rule, adults with 20 percent burns and children with 15 percent burns require intravenous fluids for treatment of actual or impending shock. Children with greater than 30 percent burns should get a central venous catheter and if the burn is over 50 percent two central lines may be required.Initial central line could be placed in burnt area saving the site in unburnt area for later placement or change of a central line site.

Initial hemodynamic stability can be obtained by few boluses of isotonic crystalloid solutions such as normal saline or ringers lactate of 20 ml/kg each untill urine out put of at least 1 ml/kg/hr is established, followed by calculation of fluid therapy according to percentage of burns.

Parklands formula may be used as follows: first 24 hours lactated ringer, 4 ml/kg/ percent BSA plus maintenance fluid requirement. Half of this volume is given in first eight hours, to include the initial fluid boluses in the first half, and second half of fluid requirement given over next 16 hours.

Early feeds via a nasogastric tube can prevent a drop in serum albumin. However, intravenous

Table 96.2: Replacement fluid formulae

Formula	*Colloid*	*Crystalloid*	*Fluid required/ day*
Evans	1 ml/kg/%	1 ml/kg/%	2000 ml
Brooke	0.5 ml/kg/%	1.5 ml/kg/%	2000 ml
Parkland Hospital	—	4 ml/kg/%	—
Massachusetts General Hospital	125 ml plasma/%	15 ml/%	2000 ml

albumin can be given in roughly 12 to 15 gm for every liter of ringers lactate solution after initial fluid resuscitation, since a drop in serum albumin is common due to capillary leak.

Choice of Replacement Fluids

As mentioned earlier crystalloids such as ringers lactate are used for initial fluid resuscitation untill shock is controlled and urine output is established at >1 cc/kg/hr. Maintenance fluid is begun in 24 hours with dextrose containing fluid with ¼ normal saline to ½ normal saline, with 20 to 40 meq/L of Kcl since potassium wasting in urine is common secondary to intense adrenal stress response. Fluid can be modified to maintain homeostasis of sodium, potassium, calcium and phosphate. Albumin and fresh frozen plasma may be used depending upon the availability and values of serum albumin and coagulation profile.

Insertion of an Indwelling Catheter

The most important parameter of the adequacy of fluid therapy is the urinary output. For this reason, a Foley catheter should be inserted into the bladder immediately upon the patient's admission.

Adequate urinary output according to age:in general > 1 ml/kg/hr

0 to 1 year	8-20 ml /hr
1 to 4 years	20-25 ml/hr
4 to 10 years	25-30 ml/hr
10 years plus	30-50 ml/hr

Central Venous Pressure

Monitoring of central venous pressure may not be required for vast majority of burns. On the other hand, with patients who have failed to respond adequately to an appropriate immediate treatment or in whom pulmonary or cardiac abnormalities exist, the monitoring of central venous pressure can be an important adjunct. A reading of 7-12 cm of water and is generally accompanied by adequate urinary output and satisfactory clinical signs (improvement in mental status, perfusion, blood pressure and reduction of tachycardia).

Renal Failure

An occasional patient is seen in whom there is scanty urine output during the initial period of fluid replacement or in whom urinary output becomes markedly reduced during the course of fluid therapy. The possibility of renal failure (acute tubular necrosis) should be kept in mind. Those patients generally have some delay in fluid therapy or inadequate fluid resuscitation.

Antibiotic Therapy

At the time of admission to the hospital, a baseline culture of the burn wound should be obtained from representative areas, and this should be repeated at regular intervals. The intact burn eschar may act as a satisfactory wound dressing for the immediate post-burn period. Invasive infection or spticemia is unlikely for the first 72 hours except with beta-hemolytic streptococcus. Majority of burn centers prescribe *prophylactic systemic antistreptococcal antibiotic therapy such as penicillin/augmentin.* Subsequent antibiotic therapy is guided by wound cultures, blood and urine culture, as well as fever course, chest radiographs. Gram positive sepsis from central line infections, but more commonly gram negative sepsis with enteric gram negatives such as E coli, Klebsiella, Pseudomonas from blood urine or wound tissue cultures should be appropriately treated with antibiotics.

Pain Management

Morphine and midazolam infusion is an excellent combination to achieve sedation, analgesia and amnesia *in mechanically ventilated patients.*

In unventilated patients intermittent morphine doses with close respiratory monitoring or, in patients with few days older burns, paracetamol, ibuprofen or tramadol may be used. In addition *burn dressing and debridement can be adequately performed giving supplemental morphine or ketamine.* In older children patient controlled analgesia using morphine infusion can be successfully administered.

Local Wound Management

The majority of flash and flame burns actually require no cleansing although adherent clothing, dirt or other foreign material should be removed by gentle cleansing with bland soap and warm water. Breaking of blisters is unnecessary during initial dressing and may actually contribute to an increased fluid loss. Chemical burns should be treated with copious water for dilution.

Decompression of Circumferential Burn

Circumferential burn of extremities should be inspected carefully for any evidence of circulatory impairment. If there is a circumferential constricting eschar of an extremity, it should be decompressed with a vertical incision extending from the uninvolved skin above to the uninvolved skin below. Since deep burns (third degree) are relatively insensitive, these incisions can often be performed in the ward without any anesthesia. The incision should be made sufficiently deep into the subcutaneous tissue to release the pressure.

Topical Agents

Since 1965, a number of topical agents which have the capability of permeating the eschar with sufficient antibacterial activity to control burn wound sepsis have been utilized. The compounds in current use are:

1. Silver sulfadiazine
2. Sulfamylon acetate, 10 percent
3. Silver nitrate, o.s. percent solution
4. Neosporin
5. Other compounds such as Iodophores (Efodine).

Silver sulfadiazine is comparable to sulfamylon in bacteriostatic effect, but patient acceptance is much higher since silver sulfadiazine is less painful on application. Furthermore, it does not have the carbonic anhydrase inhibiting capacity and is extremely low in toxicity. As a result, *silver sulfadiazine (Silvadine) is currently a widely utilized and effective topical chemotherapeutic agent.*

Surgical Management/Operative Therapy

Improvements in resuscitation have consistently presented the burn surgeon with patients who are stable 48 to 72 hours after the burn. These patients carry a variable load of dead tissue in immediate contact with healthy or injured but potentially salvageable tissue. In patients with greater than 50 percent of total BSA, there is urgency in performing surgery and covering the wound to decrease operative bleeding and minimize bacterial colonization. The administration of recombinant human growth hormone (0.2 mg/kg/day) has been shown to accelerate donor site wound healing, improves nitrogen balance, and decreases protein catabolism by raising the level of insulin like growth factors. Practical significance of use of growth hormone in burn patients is unclear.

A prospective randomized study at the University of Washington clearly showed that the practice of early excision and grafting was superior to spontaneous healing. Morever, these patients returned to work twice as fast as the nonperated group. However, extensive excision calls for greater experience and is considerably more trouble than delayed grafting in the third week.

Tangential Excision

Excision is continued until punctuate, uniform brisk bleeding is obtained. If the dermis is burned through its full thickness, tangential excision is continued into the subcutaneous fat. Raw area thus created is covered with spilt thickness skin graft. Sheets of autograft should be used if sufficient donor sites are available. Skin meshed at 1:1.0 to 1:1.5 and minimally expanded can yield excellent cosmetic results that in many cases approach those obtained with sheet grafts. Meshed grafts, in addition allow egress of subgraft fluid even with minimal expansion and can be used with excellent results in all areas except the face where the use of sheet grafts is mandatory.

Nutritional Support

The hypermetabolic state seen with burn injury results in protein catabolism, lipolysis and hyperthermia resulting in increased risk of infection and poor wound healing. General measures such as temperature control and analgesia partially control the hypermetabolic response. Appropriate nutrition, instituted early can improve mortality and the length of hospital stay. We use early feedings via nasogastric tube to deliver 15 to 40 cal/percent burn BSA in addition to basic caloric requirement.

Enteral feeds have been shown to be superior to parenteral route in preventing hypermetabolism, catabolism, and intestinal translocation of viable organisms. Early enteral feeds may lead to early achievement of positive nitrogen balance.

In general up to 6 months of age 115 cal/kg/day is usually adequate. High protein diet is required: recommended protein requirement is 2.5 gm/kg/day aminoacids with 20 percent calories coming from proteins, with nonprotein cal/N_2 ratio 100:1 to achieve normal albumin, serum protein and transferrin levels. Fat content of more than 15 percent may have an adverse effect on immmune function, particularly if it is high in omega 6 fatty acid such as linoleic acid. Omega 3 fatty acids are beneficial in decreasing wound infection rate.

A low fat, high protein, essential amino acid, omega 3 fatty acid diet has been demonstrated to decrease wound infection and hospital stay in burn patients.

Evidence favors early institution of enteral feeds in severely critically ill children with severe burns.

Morbidity: Prognosis is dependent upon the extent, depth and location of the burn injury and upon the development of complications. Initial resuscitation including care of the airway and breathing and fluid therapy to establish urine output are very important factors. Associated inhalational injury and carbon monoxide poisoning are poor prognostic factors.

Superficial (first degree) and superficial partial thickness (superficial second degree) burns below 20 percent usually heal spontaneously in a period of 7 to 14 days.

Deep partial thickness (deep second degree) if not converted to full thickness skin loss or unduly complicated by infection may be expected to heal in three to six weeks.

The time required for healing of full thickness (third degree) burns is affected by the number o skin grafting procedures required.

Practice of early excision and grafting of indeterminate burns of less than 20 percent has shown significantly improvement, in the recent years, over the conventional conservative management of the past. Mortality remains high in burn injuries involving greater than 80 percent BSA due to factors such as protein/fluid loss, infections and septicemia ARDS (Acute respiratory distress syndrome) due to inhalational airway injury, shock, sepsis.

Rehabilitation of burn patients: Deep burns heal by fibrosis, scar formation and contractures. Multiple skin grafting, tendon release operations are required in addition to regular physiotherapy.

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CHAPTER 97

Heat Disorders

Purnima Dhar

Heat disorders include a special group of critical illnesses characterized by excessive heat production, decreased heat dissipation or loss of thermoregulation. Heat disorders generally do not include fevers due to inflammatory processes and are caused by other conditions such as:

- Environmental exposure to heat
- Malignant hyperthermia
- Neurolept malignant syndrome
- Thyroid storm
- Hypothalamic/brainstem injury
- Pheochromocytoma
- Thermal burns have been discussed elsewhere in this book.

In this chapter we shall discuss pathophysiology and management of environmental hyperthermia such as heat cramps, heat exhaustion and heatstroke as well as malignant hyperthermia in children.

THERMOREGULATION

The metabolic activity of the body, mainly the liver and skeletal muscles causes the production of heat. At rest the major source is the viscera and during exercise or shivering it is the skeletal muscles.

Heat elimination occurs by four mechanisms of at transfer, i.e. radiation, convection, evaporation conduction. In normal circumstances conduction losses are negligible. The main mechanisms of ss are radiation and convection followed by tion of sweat. Therefore, the regulation of w to skin and sweat gland activity are ermoregulation and this is done in three

1. Afferent thermal sensing
2. Central regulation
3. Efferent responses

Afferent thermal inputs are from the receptors which are separate for warmth and cold. These receptors increase their firing rate in response to warmth and cold respectively.

Warmth signals travel primarily via unmyelinated C fibers while cold information travels by adelta nerve fibers, although there is some overlap. Warmth signals come mainly from the skin, abdominal and thoracic viscera, spinal cord and brain. The ascending thermal information travels in the lateral spinothalamic tract.

The *central control* of body temperature is by the hypothalamus which integrates all the thermal information which is preprocessed in the spinal cord. How the body determines absolute threshold temperature is unknown but the process appears to be mediated by nor epinephrine, dopamine, 5 HT (5-hydroxytryptamine), acetylcholine, prostaglandin E_2 and neuropetidases are released in the hypothalamus in response to the presence of pyrogens in the blood. They diffuse into the anterior hypothalamus and reset the core temperature to a higher level. This is done primarily by regulating the vasomotor tone to the skin and sweat formation. In addition there is an output to cerebral cortex that modifies the behavior in response to change in temperature. Central thermoregulatory control is intact in infants (even in somewhat preterm infants) but is frequently impaired in extremely ill patients and in the elderly.[1]

Efferent responses to heat consist of cutaneous vasodilatation; sweat formation and inhibition of muscle tone. Cutaneous vasodilatation causes shunting of blood away from the liver and splanchnic circulation. Heat is transferred from viscera and muscles to skin from where it is dissipated by conduction, convection, radiation and evaporation. Evaporation of sweat is the only mechanism by which the body can dissipate heat when the environmental temperature exceeds the core body temperature. The process is quite effective and dissipates 0.58 kcal/gm of evaporated sweat.

However, children can absorb more heat from the environment due to their larger surface area. They also generate more heat per kilogram of body weight and most importantly they do not sweat effectively until after puberty.

The efficacy of evaporation as a mechanism of heat loss depends the condition of the skin and sweat glands, ambient temperature, humidity and whether or not the person is acclimatized. Evaporation does not occur when the ambient humidity exceeds 75 percent.

Acclimatization increases the sweat production up to three times the normal, decreases the threshold for sweating and increases the capacity of the sweat glands to reabsorb sweat sodium. It is characterized by earlier onset of sweating (at a lower core temp), increased sweat volume and decreased sweat electrolyte concentration. Daily exposure to work and heat for 100 min/day results in near maximal acclimatization in 7-14 days. It is hastened by modest salt deprivation and delayed by high dietary salt.[5]

When the core temperature exceeds that provoking maximum sweating, active cutaneous vasodilatation occurs and the blood flow through the top one-millimeter of the skin can reach the active cardiac output.[2]

ENVIRONMENTAL HYPERTHERMIA

Hyperthermia and potential heat injury to vital organs can occur with prolonged exposure to hot environment especially if the humidity is also high and there is increased physical activity. Summer of 1998 was the worst heat wave to strike India in fifty years. Two thousand six hundred deaths were reported officially and unofficially the figure could be double.[3]

Children often continue to play in hot and humid environment despite warning symptoms like thirst, and dehydration makes matters worse by decreasing sweat production, which is less in children anyway until puberty. Deaths have been reported in children left in closed automobiles in the sun. Automobiles left outdoors at ambient temperatures between 30°C and 40°C with windows closed, develop temperatures up to 60° in fifteen minutes, enough to produce heatstroke in a child.[4]

MINOR HEAT ILLNESSES

Heat cramps are brief, intermittent and often severe cramps in muscles fatigued by heavy work in heat. Often occur in children doing exercises in the sun in school during the beginning of hot weather where large amounts of sweat are produced and replaced by drinking plain water in copious amounts. Characterized by cramps in most worked muscles. There may be minimal temperature elevation but hyperventilation and serum electrolyte abnormalities are absent. It is rapidly relieved by intake of salt solution prepared by adding one teaspoon of salt to 500 ml of water and giving about 20 ml/kg.

Water should be cool as it increases the intake. The same volume of 0.9 percent saline can be given intra-venously if the oral intake is not good.[6] It may be associated with fainting when it is referred to as *heat syncope*.

Heat exhaustion is a more serious form and is a precursor to heat stroke. It is characterized by increase in core temperature up to 40°C and associated malaise, fatigue, headache. The child may be irritable and anxious, but is oriented with no neurological deficit and there is no history of seizures. Tachycardia, tachypnea and hypotension are usually present. Heat exhaustion is of two types depending on weather there is associated water deprivation or salt deprivation. The former is seen more in athletes and the latter in younger children who are unable to increase their salt intake. The deprivation is usually mixed and results in dehydration, orthostatic hypotension and hypernatremia (young children may be hyponatremic). Treatment consists of removal of clothing, rest in a cool environment and 20 mls/kg of intravenous 0.9 percent saline to start with and keeping the child under observation. If hypernatremia is significant more of free water may need to be administered taking care so as not to allow serum sodium to fall at a rate faster than 2 mosm/L per hour as it can result in cerebral edema and seizures.[6]

HEATSTROKE

Heatstroke is a catastrophic life-threatening emergency that occurs when the homeostatic thermoregulatory mechanisms fail after exposure to heated environment. The body temperature is more than 40°C. Heatstroke is of the following two types:

Exertional	*Non-exertional (Classic)*
Previously healthy individual	Associated illness. Medications
Younger (unacclimatised adolescent)	Older
Exercise	Sedentary
Sporadic	During heat wave
Sweating	Anhidrosis
Hypoglycemia	Normoglycemia
DIC	Mild coagulopathy
Rhabdomyolysis	Mild CPK elevation
Acute renal failure	Oliguria
Lactic acidosis	Acidosis
Hypocalcemia	Normal calcium levels

Diagnosis is based on history of exposure to heat, signs of severe CNS dysfunction (coma, seizures, delirium). Core temperature is usually more than 40°C. It may sometimes be lower. Dry hot skin and marked elevation of hepatic transaminases.

Pathology of heatstroke is postulated to be due to a failure of the thermoregulatory homeostasis. An energy depletion model has been postulated.[7] The Na+/K+ ATPase pump accounts for 25-45 percent of the BMR (basal metabolic rate) and heat is produced during the pump activity. There is a steady state decrease in the cellular energy levels and increase in temperature. Na+ ion permeability increases and an exchange of Na+ and H+ ions occurs leading to cell swelling, fatigue, collapse. The exact temperature which cellular damage occurs varies. Full recovery has been reported despite temperatures upto 44.4-46.5°C.[8]

Neurological dysfunction is the hallmark of the condition and cerebral edema is common. Delirium, coma, bizarre behavior, opisthotonus, hallucinations, decerebrate rigidity, oculogyric crisis, cerebellar dysfunction, convulsions have all been reported. Fixed and dilated pupils and flat EEG are reported to be potentially curable although some deficit is common.[9] Circulatory failure occurs due to tremendous demands on cardiovascular system. There is a fall in SVR (systemic vascular resistance); increase in cardiac index and CVP.[10] Peripheral vasodilatation is associated with *splanchnic vasoconstriction* and ischemia. *Hepatic ischemia* results in raised hepatic transaminases. Jaundice occurs after 24 to 72 hrs. No permanent liver damage is seen in survivors.[11] *Hypoglycemia* occurs due to increased utilization of glucose and liver damage leading to impaired gluconeogenesis. Diarrhea may be there due to intense splanchnic vasoconstriction. Pancreatitis has been described too.[5] 25-30 percent of exert ional heatstroke patients and 5 percent of classical heatstroke patients may present with *acute renal failure*.[12] Presence of *lactic acidosis* in classical heat stroke is a poor prognostic sign but may not be so in exertional heatstroke. Coagulation failure seen as purpura and bleeding from various sites has a poor prognosis.[13]

Differential diagnosis should be entertained only after cooling is underway. If the patient does not wake up after cooling, a lumber puncture should be done to rule out meningitis. A peripheral smear to look for malarial parasite is also a must. Anticholinergic poisoning should also be kept in mind. If in doubt plasma transaminases may clinch the diagnosis. They will be dramatically increased in heatstroke.

Management

1. *Cooling* It is the cornerstone of management. Mortality is increased if it is delayed. Various methods have been described. Immersion in water at 0°C is fast and effective but makes monitoring and airway control difficult. Physiological body cooling units wherein the patient lies on a net and is sprayed with water at 15°C and warm air at 45°C is blown over the skin surface to keep the skin vasodilated. A spray of atomized tepid water at 40°C and blowing of air with large fans has been found to be as effective as the other two methods.[14]

2. *Airway* Its control is essential as seizures and aspiration are common. Endotracheal intubation and mechanical ventilation should be instituted.
3. *Hypotension* If the blood pressure does not come up with cooling CVP measurement should be instituted. 0.9 percent saline should be administered guided by CVP. Vasopressors and inotropes may be needed. Noradrenaline should be avoided.
4. *Avoid antipyretics* Salicylates can aggravate coagulopathy and paracetamol can increase liver damage. Alcohol sponges should not be used in children as it can get absorbed through dilated cutaneous blood vessels and may worsen the coma. Dantrolene is not effective in heatstroke.[15]
5. *Urine output* Its monitoring and administration of mannitol 12.5 g initially and 12.5 g after each liter of fluid has been recommended. It increases the renal blood flow and minimizes damage from rhabdomyolysis. Avoid dextrans and starches as they can aggravate the coagulopathy.
6. Lab Investigations. ABG (arterial blood gases), CBC (complete blood count), BUN (blood urea nitrogen), electrolytes, aspartate and alanine aminotransferases, LDH (lactate dehydrogenase), CPK (creatinine phosphokinase), lactate, Ca^{++}, PT (prothrombin time), aPTT (activated partial thromboplastin time), FDP (fibrin degradation products).
7. *Benzodiazepines* Preferably short acting ones to treat agitation due to cooling and seizures.
8. *Coagulopathy* It occurs on second and third day. There is usually an evidence of fibrinolysis but EACA (epsilon amino caproic acid) is not recommended because it can cause rhabdomyolysis.
9. *Hypoglycemia and hyperglycemia* These are both reported and should be treated appropriately.
10. *Steroids* have no role.

MALIGNANT HYPERTHERMIA

Malignant hyperthermia (MH) is a potentially fatal condition, which occurs rarely following exposure to some anesthetic drugs. The classic triad of MH consists of hyperthermia, muscle rigidity and metabolic acidosis.

Pathophysiology[16]

MH is a group of closely related hypermetabolic disorders of skeletal muscle usually subclinical that features an acute loss of control of intracellular calcium (Ca^{2+}) that results in sudden, uncontrolled increase in intracellular calcium. Normally the wave of depolarization from the muscle end plate is transferred to the sarcoplasmic reticulum(SR) resulting in a release of Ca^{2+}. This increase in Ca^{2+} removes the troponin inhibition from the contractile proteins resulting in muscle contraction. The intracellular Ca^{2+} pumps rapidly transfer the Ca^{2+} ions back into the SR, and relaxation occurs. Both these processes are energy dependent and consume ATP. The release of calcium is controlled by the junctional foot protein also known as the Ryanodine (Ry) receptor. The Ca^{2+} is brought back to normal within 30 ms of muscle contraction. This removal is essential and an aberrant termination of Ry activity has emerged as a key underlying mechanism in the etiology of MH susceptibility.[16] Rigidity occurs when unbound myofibrillar Ca^{2+} approaches the contractile threshold. Dantrolene is therapeutic because it reduces Ca^{2+} release from the SR without altering Ca^{2+} re-uptake.[16] Susceptible individuals inherit the defect and the pattern of inheritance may vary from recessive to dominant. Sporadic cases with no family history have been reported. MH has been associated with King Denborough syndrome, Duchenne's muscular dystrophy, central core disease, myotonia fluctuans and osteogenesis imperfecta.

MH is more common in children with a reported incidence of 1:14,000 compared to 1:40,000 in adults. Incidence varies from country to country and between different geographical and ethnic groups within a country. It is uncommon at extremes of age although one case of a neonate presenting with MH has been reported following its birth by cesarean section. The mother had received halothane for cesarian section.

The drugs known to trigger MH are general anesthetic agents halothane, enflurane, isoflurane, sevoflurane, methoxyflurane, ether, cyclopropane and depolarizing muscle relaxants such as suxamethonium and *decamethonium*. Intravenous anesthetics such as thiopentone and prpofol are safe as are the non-depolarizing muscle relaxants and the amide as well as the ester local anesthetics.

Clinical Syndrome

MH presentation can be acute and rapid after induction of anesthesia or on rare occasions delayed for some hours and may not become overt until the child is in the recovery room or pediatric intensive care unit. Once initiated the course is very rapid. Abnormal signs like increased expired carbon dioxide, muscle rigidity, tachycardia and fever (a rise as fast as 1°C every 5 minutes) suggest the presence of MH. Hypertension followed by hypotension, hypoxemia, cyanosis, hyperapnea, metabolic acidosis, hyperkalemia, hypocalcemia, tetany, myoglobinuria, acute renal failure and cardiac failure develop secondarily very rapidly. Dysrhythmias can occur at anytime.

Management[16]

1. *Immediate termination* of volatile anesthetic if in the operating room. Mechanical ventilation with 100% oxygen. Hyperventilation is required to wash out the excessive amounts of CO_2 being formed due to intense metabolic activity.
2. *Cooling* with ice or ice packs on the surface combined with cold-water lavage of stomach and body cavities. Cardiopulmonary bypass and cooling may be required. Cooling should be halted at 38°C to prevent inadvertent hypothermia.
3. *Dantrolene* must be given immediately in a dose of 2 mg/kg intravenously and repeated every five minutes upto a maximum of 10 mg/kg or when the symptoms have been controlled. A dose of 1 mg/kg is recommended every 10 hrs for a few doses after the symptoms have subsided to prevent a relapse.[18] It can also be used for malignant neurolept syndrome and thyroid storm.
4. *Sodium bicarbonate* for acidosis correction should be given aggressively in a dose 2-4 mEq/kg.
5. *Mannitol* infusion 0.5 g/kg along with *furosemide* to establish diuresis and prevent renal shutdown should be started early.
6. *Glucose and insulin for* hyperkalemia. $CaCl_2$ 2-5 mg/kg can be given intravenously if dysrhythmias secondary to hyperkalemia.
7. *Further therapy* is guided by blood gases, electrolytes, dysrhythmias, muscle tone and urinary output.
8. *Blood studies* to be performed at the earliest after initial treatment are CPK, liver profile, BUN, lactate, glucose, coagulation studies and serum hemoglobin and myoglobin and urine hemoglobin and myoglobin. They should be repeated depending upon the clinical course. K^+ levels must be monitored because it may be an important factor in treatment (e.g. persistently elevated K^+ levels may prevent defibrillation). Although calcium and cardiac glycosides have not been shown to trigger MH, there is a reluctance to use them due to their role in the mechanism of MH. They can be safely used if indicated, like in refractory arrhythmias due to persistent hyperkalemia and may be life saving.

Permanent neurological sequelae may occur in severe cases. Calcium antagonists are not useful and may cause harm by interacting with dantrolene and aggravating hyperkalemia.[17]

Some Clinicians Recommend Steroids

Early diagnosis and treatment of MH are essential. The complications that may arise are difficult to treat and may lead to sequelae. Finally, retriggering may occur even with dantrolene therapy as the drug is redistributed, metabolized and excreted.

SUDDEN UNEXPECTED CARDIAC ARREST IN CHILDREN

Children less than about 10 years of age who experience sudden cardiac arrest after succinylcholine in the absence of hypoxemia and anesthetic overdose ahould be treated for acute hyperkalemia. First in this situation calcium chloride should be administered along with other means to reduce serum potassium. They should be presumed to have subclinical muscular dystrophy and a neurologist should be consulted.

Postacute Phase

a. Observe the patient in an ICU setting for at least 24 hours since recrudescence of MH may occur.

b. Administer dantrolene 1 mg/kg or more every 4 to 6 hours for 24-48 hours postepisode.
c. Follow ABG, CPK, potassium, urine and serum myoglobin, clotting studies and core body temperature until such time as they return to normal values (every 6 hours). Central temperature (rectal/esophageal) should be continuously monitored until stable.

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CHAPTER

98

Electrical Shock

Soonu Udani

Electrical shock and drowning are fairly common accidents that occur to children playing with or without supervision. Fatalities occur in both situations and there are very few awareness programs or preventive measures where children play. Lightning strikes do occur and may be under reported as they may occur in rural areas, wide open spaces during electrical storms and the victim is often alone. As there are few or no external injuries, these may be passed off as "heart attacks".

Most injuries are caused during recreational activities like kite flying. Faulty electrical equipment, especially voltage leakages in wet areas are common problems in the house. Accidents also occur when power is being tapped from lines. There are commercially available "hooks" that actually are used to tap power and these can cause fatal electrical shock.

Mechanism of Electrical Injury

Electricity causes injury by three different mechanisms:

1. Direct effect of electric current on body tissue.
2. Conversion of electrical energy to thermal energy with subsequent superficial or deep burns.
3. Blunt injury caused by severe muscle contractions or falls.

Voltage, amperage, type of current, pathway and duration of contact all affect the degree of injury. Injuries that occur with voltage under 1000 V is called low voltage injury. High tension power lines have a voltage exceeding 100,000 V. Distribution lines carry 7000-8000 V and this is further stepped down to 220 V in the home. Lightning carries an electric pressure of $> 10^7$ V. In many ways, AC (Alternating current) current is worse than DC (Direct Current). There is more severe muscle contraction with tetany and the time of contact is greater; whereas, DC throws the victim off and time is shorter.[1]

Physical factors also affect severity of injury: Wet skin is better as the current tends to dissipate faster. If the victim is well grounded on metal, the injury will be very severe. A vertical path of current causes deep-seated organ damage with concentrated core damage. Ventricular fibrillation (VF) is also more common with a vertical path as the current goes through the heart. The injury is inversely proportional to the cross-sectional area of the part touched. Hence the arm is more affected than the torso for the same degree of current.

Salient features of electrical injuries[2]: Visible superficial injuries are few. Deep tissue damage can be extensive and be difficult to estimate. Therefore forensic pathologists at postmortem have described most of the pathology of electrical injuries. Muscle injury can cause life threatening myoglobinuria and renal failure.

Rescue: The first priority is to gain safe access to the victim. All switches should be put off and the power supply disconnected. If the patient is alive then he/she is likely to survive the initial period. All cardiac arrest situations should be vigorously handled. As VF is common, defibrillation is important. The resuscitation (PALS) guidelines remain the same: Airway, Breathing, Circulation. Dilated pupils at the time of rescue should not mean the end of resuscitation as autonomic changes may be the cause. Fluids may be needed at the site and during transport but lightning injuries usually do not need fluids.

Later management: This will depend entirely on the extent of injury. Myoglobinuria is treated with fluids at 1.7 times the maintenance rate with alkalinisation. Mannitol may be used. Early dialysis should be used if renal failure sets in. There may be hollow organ rupture, solid organ contusion, fractures and burns.

Burns

Electrical injuries share many characteristics with thermal burns. There are differences, however, in the way that the passage of electrical current causes tissue injury. Most tissue damage in electrical injury is due to heat generated by current flow. It is often found that deep tissue damage exceeds surface wounds observed after electrical (especially high voltage) injury.

The usual tendency in the treatment of an electrical burn is to underestimate the severity of the lesion in the early stages. In carefully selected cases, early excision and grafting may be done to advantage; however it is often impossible to judge the extent of damage, and there is possibility of either excessive resection of normal tissue or inadequate resection of irreversibly damaged tissue. These lesions should be treated conservatively until the full extent of the burns has become apparent.

Burns may be of any degree. Scald like burns may occur in flash injuries. Only small superficial punctuate areas may be seen. A feathering pattern may be seen on the skin. The percentage of burns cannot be estimated by the rule of 9. Other signs of poor perfusion like blood pressure, urine output, etc must be looked for. As there can be significant tissue oedema, fluids should be given at 1.5 times maintenance. Monitoring with invasive devices should be done if clinical judgment indicates great severity.

Central core: The center of the part in contact or the core of the body may be severely affected. The core, e.g. bone, retains heat for a longer time and hence continues to suffer damage. This heat is then transmitted to the surrounding tissues which continue to get damaged. A fairly good looking limb may actually start showing gangrene in a few days because of necrosis of the bone and surrounding muscle.

Massive local edema may develop, leading to compartment syndromes requiring fasciotomy and pressure release. There may be direct damage to the nerves and blood vessels, or coagulation necrosis, also resulting in later gangrene. A remote complication is aneurysms after vessel injury.

The heart[3]: Dysrhythmias are very common. ST elevation, ST-T changes, premature ventricular and atrial beats as well as all degrees of heart blocks may be seen. Asystole occurs more commonly with high voltage DC and AC currents. VF is more common with household injuries. When lightening strikes-cosmic cardioversion–there may be asystole. However, the inherent automaticity of the heart takes over in a few seconds and the patient recovers. If there is VF with respiratory arrest, the hypoxia will worsen and prolong the VF. Direct myocardial damage with coagulation necrosis, coronary spasm and infarct may be aggravated by massive catecholamine release.

The Central nervous system (CNS): Brief loss of consciousness is not uncommon and does not imply a poor prognosis. Accompanying trauma or hypoxia, especially after a cardiac arrest, may be the limiting feature to recovery. Spinal cord injury may occur from core damage. The prognosis for recovery is better when the signs are seen early in the course. When signs develop late, the problem is usually irreversible. Amyotrophic lateral sclerois, transient myelitis and ascending paralysis have all been reported.

Other organ damage: Visceral rupture is a rare problem but must be kept in mind if there are abdominal signs. Coagulation necrosis of any organ may occur. Long term problems may be cataracts and Horner's syndrome. The tympanic membrane may rupture or inner ear complaints of tinnitus and vertigo may persist.

SUMMARY

Prevention of all injuries remains crucial. Stricter laws are implemented. Supervision of children at all times while playing is essential. Warning signs should be clear and understandable. Awareness and education of the lay public and health care workers is crucial

First aid and basic CPR should be taught at the high school level routinely. Children themselves should be made aware of the hazards. Timely intervention should be available with trained paramedical staff and quick transport facilities. Emergency rooms should be geared to treat victims of all kinds of accidents.

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Section Twelve

Miscellaneous

CHAPTER 99

Research in the Pediatric Intensive Care Unit

Praveen Khilnani

Planning a clinical study design and application of basic research methods, analysis, interpretation of data, presentation of scientific paper and publication of scientific data in peer reviewed journals should be an integral part of the training in pediatric critical care medicine.

Purpose of this chapter is to familiarize the reader with basic clinical study designs, rationale and application of statistical methods to analyze data, and finally helpful hints on how to get published in a peer reviewed scientific journal.

Evidence-based Medicine

In this era of evidence-based medicine every one ques-tions. Where is the evidence?

Various classes of scientific evidence have been described to draw inference from a particular study. Double blind, prospective, randomized, placebo controlled evidence remains the best (class I evidence).

Classes of Evidence

The Class I, IIa, IIb, III and Indeterminate designations after many guidelines indicate the strength of evidence that supports the guidelines.

Class I : Guidelines are supported by excellent, definitive evidence of effectiveness in humans.

Class IIa : Guidelines are supported by very good evidence of effectiveness and safety in humans and are highly recommended interventions and actions.

Class IIb : Guidelines are supported by fair to good evidence of effectiveness and safety in humans with no evidence of harm.

Class Indeterminate: Interventions or actions are proposed guidelines with insufficient evidence to support a final recommendation for clinical use.

Class III : Interventions or actions are not useful, may be harmful and thus are unacceptable.

A working knowledge of basic concepts biostatistics (discussed in this chapter) is important for organization, analysis, interpretation and presentation of numerical information (data). Reader is referred to texts of biostatistics for detailed calculations.

Statistics

A body of techniques and procedures dealing with the collection, organization, analysis, interpretation, and presentation of information that can be stated numerically.

Task of a Statistician

1. Guide and design of an experiment or survey with a minimum of bias.
2. To analyze data.
3. To present and interpret results.

Results are best evaluated in terms of probability statements that will facilitate the decision making process.

Variables: Various characteristics such as age, weight, height are referred to as variables. A variable can be stimulus variable (i.e. smoking) or an outcome variable (prematurity).

Data: Values of observation recorded for variables are referred to as data. Data are the raw material of statistics.

Data collection can be retrospective or prospective.

Retrospective Studies (Case Control Studies)

Retrospective studies gather past data from selected cases (individuals with disease or condition) and controls (individuals without that disease or condition) to determine differences.

Advantages of retrospective studies is that they are economical and useful for studying rare diseases. Main disadvantages include in incomplete data which were collected for some other purpose.

Prospective Studies (Cohort Studies)

Example

A group of healthy people followed over a certain period to determine disease frequency (lung cancer). Group is divided according to presence or absence of stimulus variable (smoking) (Table 99.1).

Advantage: Bias can be controlled.

Disadvantage: Prospective studies are expensive, time consuming, and not useful for studying rare diseases.

Table 99.1: Generalized 2 × 2 table

Stimulus variable	*Outcome variable*	
	With disease	*Without disease*
Absent	a	b
Present	c	d

- Stimulus variable smoking
- Outcome variable (disease–prematurity)

Typically ratios compared are:

a/a + c and b/b + d :	For retrospective study, i.e. were mothers of premature infants more likely to have been smokers than mothers of normal infants.?and
a/a + b and c/c + d :	For prospective study, i.e. which group has higher frequency of premature babies, mothers who smoke or mothers who don't?

Clinical Trial

A carefully designed experiment that seeks to determine, under control conditions, the effectiveness of a new drug or treatment method.

Two groups consist of Treatment group and Control group. Treatment group receives the test drug and control group receives the placebo (a pill that does not contain the test drug). Subjects or patients get randomly allocated to each group to limit bias.

- Single blind trial : Patient does not know which group he is in.
- Double blind trial : Neither the patient nor the investigator knows which group a particular patient belongs to.

Control must be consisting of subjects from the same pool and at the same time.

Such a trial conducted prospectively is known as:

- Randomized double blind placebo controlled trial.
  - Population and sample: Population is a set of persons (or objects) having a common observable characteristic. A sample is a subset of population.
  - Randomization: Random sampling can be done by use of frequency tables (Table 99.2)
  - Results: Results of a clinical trial can be presented as graphic data as shown in Figures 99.1 to 99. Graphic data presents an instant overview of the results.
    i. Histograms (Fig. 99.1)
    ii. Frequency polygon (Figs 99.2 and 99.3)

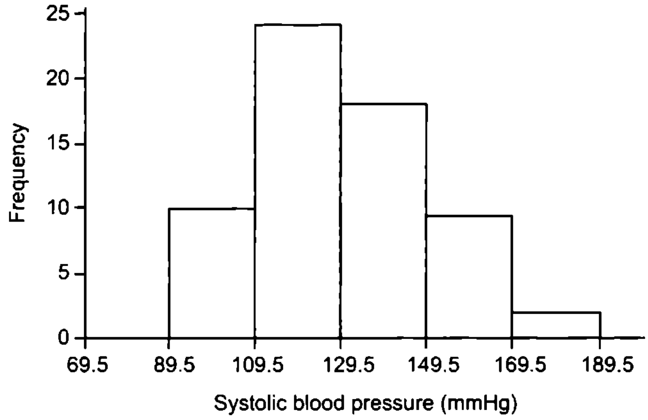


Fig. 99.1: Histogram illustrating data. Systolic blood pressure of a sample of 63 nonsmokers from the Honolulu Heart Study

Table 99.2: Random numbers

					col. 31 ↓					
00439	81846	45446	93971	84217	74968	62758	49813	13666	12981	
29676	37909	95673	66757	72420	40567	81119	87494	85471	81520	
69386	71708	88608	67251	22512	00169	58624	04059	05557	73345	
68381	61725	49122	75836	15368	52551	54604	61136	51996	19921	
69158	38683	41374	17028	09304	10834	61546	33503	84277	44800	
00858	04352	17833	41105	46569	90109	14713	15905	84555	92326	
86972	51707	58242	16035	94887	83510	56462	83759	68279	64873	
30606	45225	30161	07973	03034	82983	78242	06519	96345	53424	
93864	49044	57169	43125	11703	87009	76463	48263	99273	79449	
61937	90217	56708	35351	60820	90729	90472	68749	23171	67640	
94551	69538	52924	08530	79302	34981	12155	42714	39810	92772	
79385	49498	48569	57888	70564	17660	50411	19640	07597	34550	
14796	51195	69638	55111	06883	13761	53688	44212	71380	56294	
79793	05845	58100	24112	26866	26299	74127	63514	04218	07584	
98488	68394	65390	41384	52188	81868	74272	77608	34806	46529	
96773	24159	28290	31915	30365	06082	73440	16701	78019	49144	
18849	96248	46509	56863	27018	64818	40938	66102	65833	39169	
71447	27337	62158	25679	63325	98699	16926	28928	06692	05049	
97091	42397	08406	04213	52727	08328	24057	78695	91207	18451	
56644	52133	55069	57102	67821	54934	66318	35153	36755	88011	
60138	40435	75526	35949	84558	13211	29579	30084	47671	44720	
80089	48271	45519	64328	48167	14794	07440	53407	32341	30360	
54302	81734	15723	10921	20123	02787	97407	02481	69785	58025	
61763	77188	54997	28352	57192	22751	82470	92971	29091	35441	
25769	28265	26135	52688	11867	05398	43797	45228	28086	84568	
80142	64567	38915	40716	76797	37083	53872	30022	43767	60257	row
69481	57748	93003	99900	25413	64661	→ 17132	53464	52705	69602	←
40431	28106	28655	84536	71208	47599	36136	46412	99748	76167	27
16264	39564	37178	61382	51274	89407	11283	77207	90547	50981	
19618	87653	18682	22917	56801	81679	93285	68284	11203	47990	

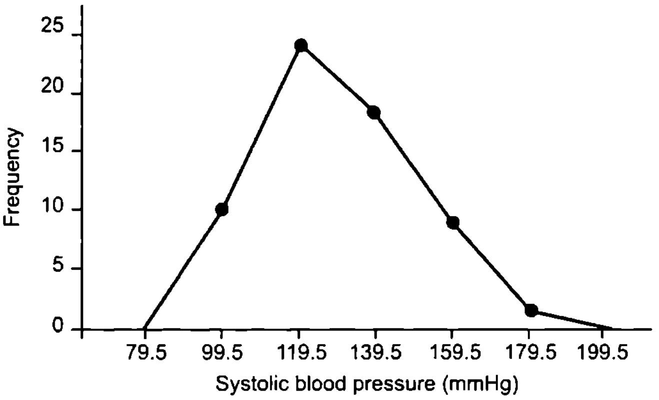


Fig. 99.2: Frequency polygon illustrating the data. Systolic blood pressure of a sample of 63 nonsmokers from the Honolulu Heart Study

iii. Bar chart (Fig. 99.4)
iv. Pie chart (Fig. 99.5).

Summarizing Data

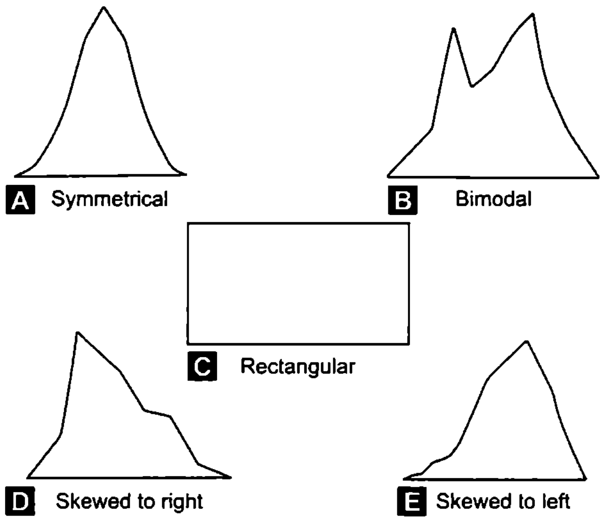
Central Tendency

The tendency of a set of data to center around certain numerical values (Figs 99.6A and B).

$$\text{The mean} : \frac{\text{Sum of all observations}}{\text{Number of observations}}$$

Median

Observation that divides distribution into equal halves.



Figs 99.3A to E: Various shapes of frequency polygons

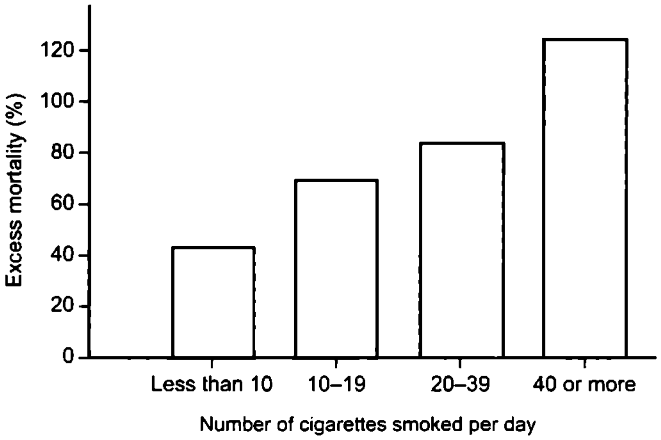


Fig. 99.4: Bar chart of excess mortality of smokers over nonsmokers according to number of cigarettes smoked

Mode

Most frequently occurring observation

- In a normal distribution of data mean = median = mode
- If the distribution is skewed then median represents a typical observation.

Range

Difference in highest and the lowest value.

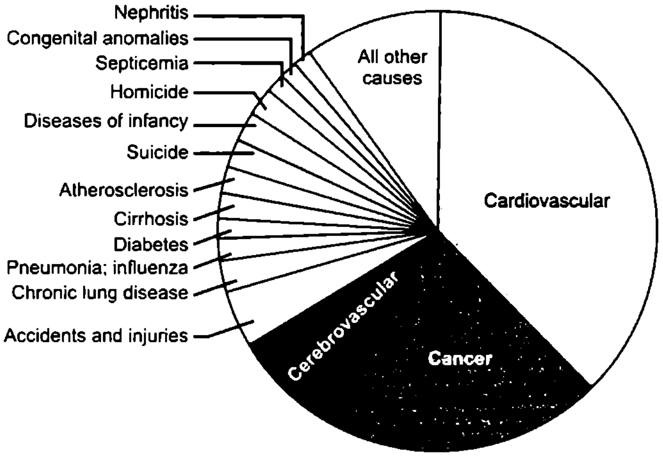


Fig. 99.5: Pie chart of leading causes of death in the United State, 1979 *(Source: National Center for Health Statistics–1982)*

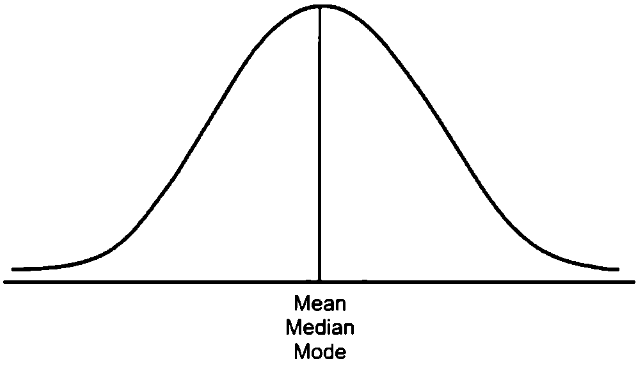


Fig. 99.6A: Symmetrical frequency distribution

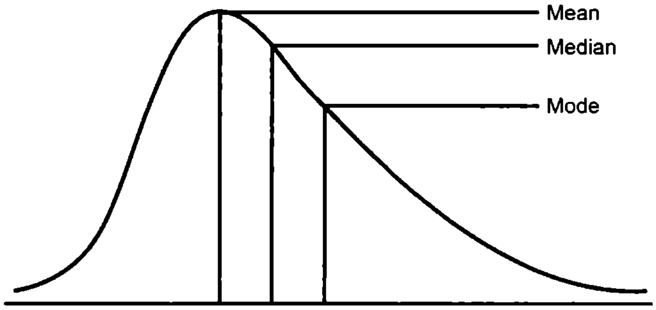


Fig. 99.6B: Asymmetrical distribution, Skewed to the Right

Mean Deviation

Average deviation of all observations from the mean is:

Standard deviation (SD) (square root of variance)

Variance: It is squaring of each deviation from mean, then summing it up and divide by number of observation. Square root of this value is standard deviation.

Coefficient of variation: The ratio of SD to mean expressed as percentage. It depicts size of standard deviation relative to its mean.

Students T test: It is used for small samples of paired data when SD is not known.

Statistical Significance

This is a test used to put the data collected in perspective and make it easy for the investigator to know what it means.

Null hypothesis: A claim that there is no difference between the population mean and the hypothesized value.

If null hypothesis is rejected the data is considered statistically significant. A value of probability is given to signify the statistical significance.

- +b $P < 0.05$ means that probability of event/finding +d occuring by chance alone is less than 0.05 percent,
- and $p < 0.01$ means that probability of event/finding occurring by chance alone is less than 0.01 per cent.

Therefore, smaller the p value greater is the statistical significance.

Type I error: When null hypothesis is true but erroneously rejected (findings could actually occur by chance alone, not evident from results of the study) probability of that is type I error.

Type II error: It occurs when null hypothesis is false but erroneously accepted (significant findings getting ignored due to mistakenly taken as a chance finding) probability of that is type II error.

Increasing Sample Size can Reduce Errors

Power of a statistical test is determined inversely by the chance of type I and type II errors.

Analysis of Variance (ANOVA)

It is a powerful method to analyze differences among a number of groups. It deals with comparison of means from several groups. T test can only be done in two groups. It tests "Within group variance" and "Between group variance".

Chi Square Test

Chi square test compares observed frequency with expected frequency for qualitative data. An example being association between smoking and drinking during pregnancy (Table 99.3).

It must be used to compare independent observations.

It is computed as the sum of ratios of squared differences to expected values.

Table 99.3: 2 × 2 Contingency table

[illegible]	[illegible]	[illegible]	[illegible]
Yes	a	b	a + b
No	c	d	c + d
	a + c	b + d	a + b + c + d = n

Measuring Strength of Association

Table 99.4: 2 × 2 table for measuring relative risk

[illegible]	[illegible]	[illegible]	[illegible]
Present	a	b	a + b
Absent	c	d	c + d

Relative risk: It can be calculated from Table 99.4 a this is also referred to as

Odds ratio: Odds in favor of having a particul disease. Another version of this odds ratio is t *relative odds* used for retrospective studies. Th provides an estimate of the relative risk.

Relative Odds (O)

$$O = ad/bc$$

Correlation and Linear Regression

This test is used to measure relationship betwe two quantitative variables.

Linear correlation: Measure and strength of bivari association.

Linear regression: It is used to predict the degree of relationship between the two quantitative variables: (y) dependent outcome variable for (x) independent input variable.

Correlation coefficient (r): Measures strength of the relationship between the two variables, provided the relationship is linear.

Scatter diagrams are shown in Figures 99.7 and 99.8.

As shown in Figure 99.7 a regression line (line of best fit) is obtained. (r) is expressed as pearson correlation coefficient. The closer the points to the line of best fit the coefficient becomes close to 1.

As shown in Figure 99.8 in various scatter diagrams, the coefficient becomes smaller and smaller as points cluster less closely around the line.

r = +1 (perfect positive correlation).

r = –1 (perfect negative correlation).

r = 0 (no relationship between variables).

Limitations of Linear Regression

It does not measure strength of nonlinear relationship. A high correlation can be easily mistaken as a cause and effect relationship.

Slope of regression line (regression coefficient) gives good indication of relationship between x and y.

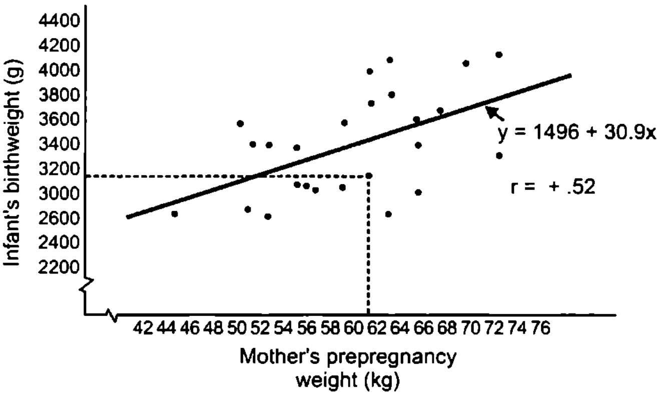


Fig. 99.7: Scatter diagram of Infants' birthweights relative to mothers' prepregnancy weights

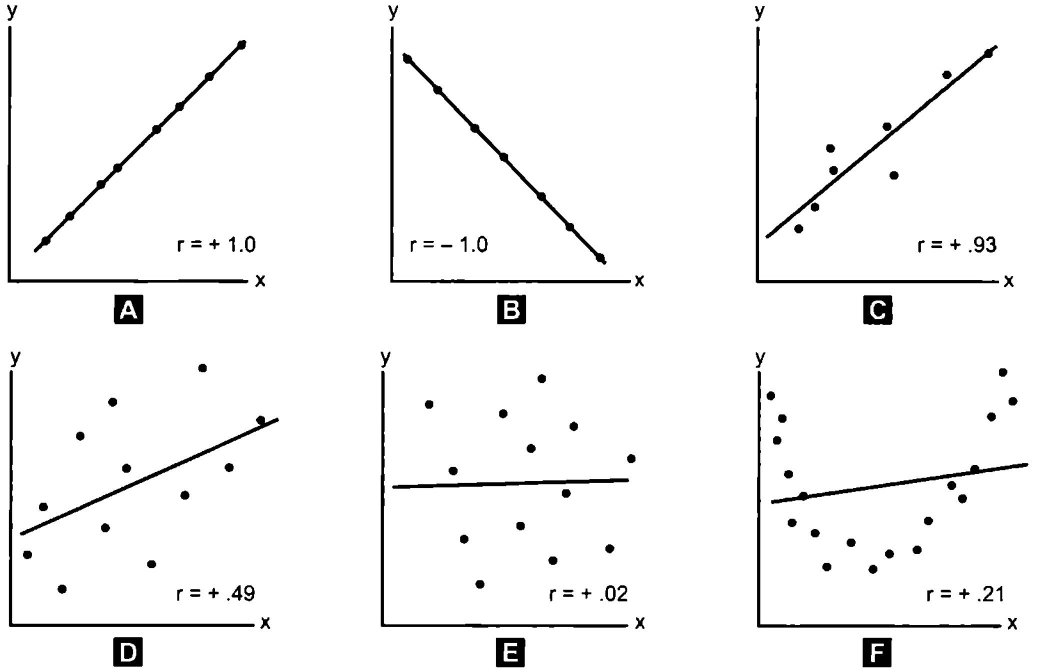
The statistical methods discussed above were parametric methods.

Nonparametric Methods

These methods are used for data where distribution is unknown.

Wilcoxson rank sum test: Similar to T test for two independent samples.

Wilcoxsan signed rank test: Similar to T test for two dependent samples.



Figs 99.8A to F: Examples of various values of r

Spearman rank order correlation coefficient is used to describe association of two ranked variables.

Publishing in Critical Care Literature

Following discussion involves evaluation of scientific study (paper) submitted for publication.

Evaluation

Major objective is to look for, and rule out BIAS in the study that would significantly affect the inference drawn from the results.

Various types of bias are described.

Observer bias: Observer may subconsciously attribute certain characters to the subject. The result of observer bias is that those characteristics are more likely to be recorded for cases than for controls.

Sampling Bias

- *Convenience sampling* involves chosing easy to find subjects.
- *Systematic sampling* involves chosing every month person from the list. This can carry subtle error if the list has cyclical pattern.

Selection Bias

Selection bias exists if cases and controls were not drawn from the same population.

Response Bias

When participation is voluntary: Persons who chose voluntarily are known to differ.

Drop out Bias

Persons who drop out are known to differ:

- *Memory bias:* In surveys recent events seem to be remembered correctly, but past events may be distorted or blown out of proportion in severity.
- *Participant bias:* Knowledge of being in the experimental or control group causes this bias.

Evaluation of Scientific Methods

Objectives, Study design, Data collection, Results, Data analysis, Discussion of results and Conclusion.

Objectives

Does research report clearly state its objectives, and do conclusions address same objectives.

Study Design

What type of study? Retrospective, Prospective, Inter-ventional or observational.

Was sample selection random? Were cases and controls drawn from same reference group (population)? Single blind or double blind.

Data Collection

Were diagnosis criteria clearly defined? Were outcome criteria clearly stated? Were research instruments standardized. Can this study be independently replicated?

Results

Are results presented clearly and quantitatively? Do tables and figures agree with the text? Are various tables consistent with each other.

Data Analysis

Were statistical tests appropriate? Is there statistical significance? Can reasonable inference be drawn? Does author give alternative explanation for spurious statistical significance.

Conclusion

Are findings justified by the data? Do findings relate to objectives set forth?

How to Get Published: Some Helpful Hints

Despite a well conducted study design, data collection and statistically significant results, the research paper may not be selected for publication. Following are some helpful hints to keep the editorial board reviewer interested in your paper.

1. All research related points (for evaluation of a research paper) mentioned above should be considered in detail.
2. A good proofread, grammatically correct, to the point, nonrepetitive, paper written in an

organized way as per authors instructions published by the journal, can go a long way.

3. Title of the paper should match the content.
4. Abstract a well-organized structured abstract is essential. Its contents must match the conclusion.
5. Introduction can make or break the article.It should be good quality and not too long.
6. Objectives as mentioned clear objectives and a hypothesis is a must.
7. Methods should be clearly described, as well as institutional review board approval and funding financial interests.
8. Results: Data presented should be clear. Do not repeat information in figures and tables in the text. Tables should have a title. Figure should have legends. Do not overstate the results.
9. Discussion: Analyze the results. Describe an appropriate literature review. Embellish the literature. Mention limitations of the study.
10. Conclusion: Mention key message/messages
11. References MUST be accurate.
12. Proof read the entire paper before submission, and have it read by an experienced author with good command over English language before submission. Typographical errors and poor language are irritating to the reviewer.

Remember the reviewer is doing a voluntary job and deserves better.

CHAPTER

100

Quality in Pediatric Intensive Care Unit

Praveen Khilnani

Every Medical Center strives to deliver patient care which is optimal, customer-focused, and achieves improved patient health outcomes, with minimal or no complications. The primary goal of the Quality Improvement program is the ongoing improvement of the delivery, quality, efficiency, and outcome of patient care and services. This is accomplished through a systematic examination of information provided through ongoing monitoring, evaluation and improvement activities. All quality activities are done in accordance with standards of professional health care practices, regulatory, and licensing agencies, and support the overall medical center mission and strategic plans.

Improve Patient/Parent Satisfaction

Total Quality

Two components are identified for hospital overall quality.

Quality in fact:

- Competent doctors
- Accurate medication system
- Safe care
- Curing illnesses
- Good intensive care units
- Effective anesthesia

Quality in perception:

- Value for money
- Clean rooms and toilets
- Good food
- Friendly, curtious medical and nonmedical staff
- Television reception
- Comfortable sleep/toilet facilities for parents
- Hospital architecture

So, general components of quality include:

- Assessment of patients by doctors, nurses and other team members
- Planning, implementing, evaluating the medical plan of care
- Administration of medications
- Administration of treatments and therapies
- Patient and family education

Doctors should be qualified well trained and certified by medical council of India as well as state council.

Nursing care needs to be provided on a 24-hour basis to patients from infancy to old age, encompassing health-care needs which span the continuum of care. Efficient Nursing care should be provided in various settings including patient care units; inpatient and outpatient surgery; and the Emergency Department. Providers of nursing care should include Professionally qualified Nurses, assistive personnel and nursing students (if applicable).

The Pediatric Intensive Care Quality Improvement Program

It should be designed to enhance patient care through systematic assessment and improvement of the quality and appropriateness of care rendered by the team members. Opportunities to improve patient care through evaluation of clinical and operational performance measures should be integrated into ongoing management processes.

Hospital quality program goes hand in hand with individual hospital services as it affects the functioning of all the services including the pediatric intensive care unit. Pediatric continuous quality improvement (CQI) committee should comprise of medical incharge, nursing incharge, administrative representative, representative from lab, radiology and other affiliated services.

Review Process

The Scientific Method may be employed in identifying general quality indicators and measuring processes. The PDCA model of the scientific method is useful in the medical center CQI (continuous quality improvement).

- P—Plan:
  - Identify critical processes
  - Identify users (patients) of these critical processes
  - Identify users requirements
  - Define the quality indicator (operational definition)
  - Devise a data collection plan, including methodology and analysis
- D—Do:
  - Collect data on quality indicato
- C—Check:
  - Analyze results of data collection (benchmarking, internal comparison, etc.)
  - Identify gaps in quality
- A—Act:
  - Implement CQI tools to improve process outcomes
  - Summarize the indicator's performance and the implementation/application of QI for making improvements on a regular basis
  - Identify exceptions/barriers
  - Advance unresolvable issues to Administrative Liaison for follow-through:

As a component to CQI, regular morbidity and mortality meeting are important.

Various Quality Issues Specific to the PICU

CQI (continuous quality improvement) committee should address following issues regularly (mentioned below in no particular order)

- Patient/parent complaints regarding facilities, medical care and nursing care
- Lab turnaround time
- Accidental extubation.
- Endotracheal tube disconnection, kink, and right mainstem intubation, iatrogenesis pneumothorax.
- Ventilator malfunction due to power failure and non-charged battery
- Central and invasive line care
- Enforcement of visitation policy
- Minimizing drug administration errors
- Extravasation of medications causing skin or limb injury visitation control
- Infection control and enforcement of hand washing protocol
- Transport adverse events
- Efficient portable safe investigations, X-rays, ECG, ultrasounds
- Blood product and blood bank services
- Pain control
- Fall from bed
- Pressure sores
- Occipital ulcers
- Oximeter probe injury
- Tape injury
- Fecal impaction
- Overheating or hypothermia
- Close monitoring of alarms correlation with deterioration in medical condition of the child is an extremely important quality indicator.

Reporting

Incharge of the PICU and Director of Nursing should be responsible for reporting to the Administrative Liaison on key quality indicators and their impact on improvement, or potential action plans for unresolved issues.

SUMMARY

This is a new field in India and as more and more private sector hospitals are coming up with intensive care services, a quality improvement process should be established to improve patient care, minimize complications, make it cost efficient (value for money) and prevent consumer (CPA) law suits/claims for damages or injury.

CHAPTER

Training in Pediatric Critical Care Medicine

Praveen Khilnani

In countries like India where pediatric intensive (critical) care medicine is in a rapidly growing and advancing mode, proper training in the field is a great necessity.

Pediatricians who have had a postgraduate training in pediatrics after graduating from the medical schools are the usual candidates to choose advanced training in this field. PALS certification is a prerequisite to enrolling in such a program. Experience in working in a PICU after postgraduation in pediatrics is preferred.

Pediatric section of the Indian society of critical care medicine and the Intensive care chapter of the Indian academy of pediatrics have begun a fellowship program in the field of pediatric intensive care (See curriculum). Recently DNB program in pediatric critical care medicine has been approved to be of two years duration.

Components of training are an evolving process leading to training a candidate in eventually leading a new pediatric critical care program.

Components of Training

Didactic teaching sessions as per the curriculum (see Appendix).

Hands on training In life saving procedures such as cardiopulmonary resuscitation, airway management including bagmask ventilation, use of laryngeal mask airway, endotracheal intubation, vascular access (peripheral and central), introsseous line placement, arterial line placement, needle thoracostomy, chest tube placement, pericardiocentesis, defibrillation, and external cardiac pacing. Carrying out a pediatric critical care transport.

Clinical Skills Acquired in the PICU

Rapid cardiopulmonary assessment and triage of critical versus less critical patient. Prioritizing treatment and laboratory investigations: Airway management, ventilation, fluid therapy and inotropic support, arrangement of blood products in a bleeding patient, arranging for stat CT/ultrasound, getting appropriate medical and surgical specialist consults in order of priority.

Analysis of clinical and laboratory data to lead to a working diagnosis and formulating the treatment plan.

Organized problems/system oriented approach to case presentation on daily clinical rounds.

Besides above mentioned components, the training of a pediatric intensivist must include the following components.

Communication

Communicating with various specialists involved in care of the critically ill child.

Developing capability of working as a team with multidisciplinary collaborative approach, with nursing, dietary, physical therapy, radiology, etc.

Communication with referring pediatrician regarding patient condition.

Communication with parents regarding patient progress and care plan. Dealing compassionately with families of a dying child, end of life care issues.

Teaching Skills

Case presentation and educational seminars presented by the candidate in departmental educational meetings are ideal for learning the teaching skills, public speaking.

Teaching residents in small groups during clinical rounds.

Teaching nurses in practical aspects of pediatric critical care.

Quality Improvement

- Learn infection control
- Learn safety
- Learn to reduce morbidity, and mortality
- Learn outcome assessment.

Legal Aspects of Pediatric Critical Care

Knowledge of consumer protection act medical negligence and malpractice.

Knowing procedures of medicolegal cases (for example, cases requiring autopsy).

Death Certification

Acting in the best interest of patient within legal limits and practice standard of care medicine.

Informed consent for all treatment and procedures.

Planning Clinical Research

Should learn to plan and carryout clinical studies with consent of the institutional review board (ethics committee).

Learn literature search: Learn basic biostatistics for compiling, analyzing and presentation of data.

Learn to write a research paper, a case report, a review article. Present clinical research paper.

Leadership

Directing a new pediatric critical care program.

Know guidelines on unit design, admission, discharge criteria.

Know PICU economics: cost of equipment, treatment, hospital, intensivist fee structure.

Develop Treatment Protocols

Data collection on census, ventilator days, diagnosis, demographics, adverse events, mortality and morbidity

- Develop pediatric critical care transport program.
- Develop outreach marketing.

APPENDIX

Curriculum Approved by Pediatric Critical Care Council (A joint body of IAP and ISCCM)

SKILLS

All of the following skills as applicable to practice of Pediatric Critical Care.

Respiratory

Maintenance of open airway, suctioning the airway endotracheal intubation (oral and nasal)

- Cricothyrotomy
- Placement of an intercostal tube
- Ventilation by bag and mask
- Setting and changing modes of ventilation as per needs
- Weaning from mechanical ventilation
- Interpretation of arterial and mixed venous blood gases
- Tracheostomy (desirable)
- Interpretation of pulmonary function tests including bedside spirometry (desirable).

Cardiovascular

- ECG interpretation
- Placement of central venous catheter (by different routes) placement of arterial catheter (by different routes)
- Implementation of cardiovascular support (inotropic therapy) Pericardiocentesis in acute tamponde
- Antiarrhythmic therapy
- Cardioversion and defibrillation thrombolysis
- Placement of swan ganz catheter (desirable).

Neurologic

- Basic interpretation of CT Scan/MRI, EEG
- Brain death protocol-calorie test, apnea test
- Intracranial pressure monitoring (desirable).

Metabolic and Nutritional

- Implementation of intravenous fluid therapy, enteral and parenteral nutrition.

Hematologic

- Interpretation of a coagulation profile and correction of homeostatic coagulation disorders (anticoagulation and fibrinolytic therapy). Implementation of blood component therapy.

Renal

- Bladder catheterization,
- Peritoneal dialysis,
- Renal support techniques (desirable).

Psychosocial

- An Understanding of the effect of life threatening illnesses on patient and their families, and death and dying, and effectively communicate with the child and the family.

General

- Has acquired skills in educating medical and paramedical professionals.
- Has acquired skills in handling the PICU equipments.
- Is oriented to principles of research methodology.

SYLLABUS

i. *Emergency resuscitation and acute airway management*
  - Cardiopulmonary resuscitation
  - Airway management in pediatric critical care
  - Transportation of Critically ill children.

ii. *Respiratory failure*
  - Developmental physiology of Resp. System.
  - Upper airway obstruction, including foreign bodies, infection and bums
  - Lower airway disease: bronchiolitis and asthma
  - Acute respiratory distress syndrome (ARDS)
  - Neuromuscular disease and respiratory failure.
  - Chronic lung disease in infants and children
    - Principles and practice of Respiratory support, mechanical ventilation and weaning.
    - Respiratory monitoring (pulse oxitnetry, capnography)
    - Oxygen therapy.

iii. *Cardiac and circulatory failure*
  - Developmental cardiovascular physiology
  - Cardio respiratory interactions
  - Arrhythrnias and their management
  - Shock and multi organ system dysfunction
  - Hypertensive emergencies
  - Cardiogenic pulmonary edema, cardiomyopathies
  - Postoperative management of the cardiac surgical patient
  - Unusual causes of myocardial ischemia, pulmonary edema and cyanosis hemodynamic monitoring relevant to pediatric critical care.

iv. *Neurologic intensive care*
  - Evaluation of a comatose child
  - Pathophysiology and management of raised intracranial pressure monitoring of central nervous system
  - Theories of brain resuscitation
  - Meningitis, infectious encephalopathies and other central nervous system infections.
  - Status epilepticus

  - Reyes syndrome and metabolic encephalopathies
  - Head and spinal cord injury
  - Cerebrovascular disease and vascular anomalies
  - Pediatric drowning and near drowning
  - Brain death, organ, donation and withdrawal of life support.

v. *Immunologic and infectious disease considerations*
  - Overwhelming sepsis, SIRS, MODS
  - Severe infection due to aerobic and anaerobic bacteria, viruses, fimgal and parasites.
  - Primary and secondary immunodeficiency
  - The critically ill child with human immunodeficiency virus (HIV) infection nosocomial infections
  - Principles of antibiotic selections and dosage schedules for immunotherapy in critical illnesses.

vi. *Nutrition and gastrointestinal emergencies*
  - Nutiriton and metabolic changes in critical illness
  - Principles of enteral and parenteral nutrition
  - Gastrointestinal and heptic failure
  - GIT bleeding, peritorities
  - Issues in liver transplantation
  - Abdominal trauma, abdominal surgery, bowel obstruction

vii. *Renal, endocrine and metabolic disorders*
  - Acute renal failure and renal replacement therapy
  - Renal disorders requiring intensive care
  - Endocrine, mineral and metabolic disease in pediatric intensive care

viii. *Hematologic and oncologic*
  - Principles of anticoagulation, fibrinolytic therapy and blood component therapy.

ix. *Specific poisonings and environmental emergencies*
  - Intensive care management of common poisonings.
  - Environmental hazards: hypo-and hypertherrnia, near drowning, electrocution, radiations, chemical injuries, animal bites.

x. *Surgical and anesthetic considerations*
  - Multiple trauma in the pediatric patient
  - Neuroendocrine response to stress
  - Analgesia, sedation and postoperative management in the pediatric ICU
  - Principles of neuromuscular blockade in the critically ill patient.

xi. *PICU administration*
  - Pediatric intensive care nursing
  - Continuous quality improvement in the pediatric intensive care unit
  - Ethical and legal aspects of critical care including 'Do not resuscitate' orders, principles of informed consent, withholding and withdrawing life support, organ donation.
  - Outcome analysis including measurement of severity of illness using PRISM, PIM and TIS scores.

xii. *General*
  - Pharmacology, pharmacokinetics and drug interactions
  - Transport of the critically ill child
  - Management of the organ donor
  - Participation in regional and national CME's seminars and conference in critical care and affiliation with such critical care organization is desirable.

CHAPTER

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Medicolegal Aspects in Intensive Care

Uttara Babbar, Sidharth Luthra

This opinion has been drafted as a note clarifying the position of law on medical negligence, covering the issues of consent, malpractice and the application of the Consumer Protection Act to doctors. After a general understanding of these issues, the paper then seeks to apply the same in the extremely specific context of the duty of a medical practitioner towards patients in the Intensive Care Unit, especially sick children and the principle of consent therein.

Medical Negligence

What amounts to medical negligence? When can a doctor be said to be negligent in the performance of his duties? What is the standard of care that a doctor is expected to meet in his practice?

For a claim for compensation upon negligence to be established, it needs to be proved that:

a. the defendant owed a duty of care to the consumer;
b. there has been a breach in the performance of that duty;
c. there should be some consequent loss caused to the person.

The Supreme Court of India has held in *Dr Laxman Bal Krishan Joshi* vs *Dr Drimbak Bapu Golbole and Another*[1] that

"The duties which a doctor owes to his patient are clear. A person who holds himself out ready to give medical advice and treatment impliedly undertakes that he is possessed of skill and knowledge for the purpose. Such a person when consulted by a patient owes him certain duties, viz, a duty of care in deciding what treatment to give or a duty of care in the administration of that treatment. A breach of any of those duties gives a right of action for negligence to the patient. The practitioner must bring to his task a reasonable degree of skill and knowledge and must exercise a reasonable degree of care.

Neither the very highest nor a very low degree of care and competence judged in the light of the particular circumstances of each case is what the law requires. The doctor, no doubt, has a discretion in choosing treatment which he proposes to give to the patient and such discretion in relatively higher in cases of emergency".

The issue of medical negligence has been dealt with in great detail in the case of *Bolam* vs *Friern Hospitals Committee,*[1] wherein McNair J held that "in the case of a medical man negligence means failure to act in accordance with the standards of reasonably competent medical men at that time". The same Judge also held that "there may be one or more perfectly proper standards, and if the medical man conforms with one of those proper standards he is not negligent". A doctor is not guilty of negligence if he has acted in accordance with a practice accepted as proper by a responsible body of medical men.

Here, it should be pointed out, that what amounts to reasonable conduct will have to be decided upon by the Court and not by the profession, though what other professionals do in similar situations will be a valid consideration to be weighed by the Court.

Balancing of Risks

It is important to take into account the purpose of the defendant's conduct to assess what is reasonable. If his actions were sufficiently important, then it would justify the assumption of abnormal risk.[2] This proposition cannot always imply that the purpose of saving life can justify taking any risk. The risks have to be balanced against the consequences of not taking the risk. They also have to be weighed in light of the expected benefits to the patient. Thus, if the chances of a patient's survival are not very high, it would justify taking greater risks and vice versa.[3]

Criminal Negligence

In Criminal Law, cases relating to the medical profession mostly consist of allegations of negligence or a lack of duty to take adequate care which would be acts on a lower plane as compared to traditionally known offences like murder, culpable homicide not amounting to murder, causing grievous hurt etc. as the requisite intention would be lacking. However, criminal law takes into its fold acts that may be negligently done, and it may still be possible for a medical professional to commit an offence in discharge of his professional duties.

Criminal negligence is gross and culpable neglect—a failure to exercise that care and failure to take precaution which having regard to the circumstances, it is the imperative duty of that individual. There are various offences in the Indian Penal Code which pertain to doctors, but the specific provisions that deal with negligence, *per se*, are Sections 336 to 338 and Section 304A. Sections 336 to 338 deal with rash and negligent acts which may cause injury/ grievous hurt. These kinds of cases/allegations will be on the increase in cases where the patient suffers injuries on the body as a result of the procedure conducted upon him, and the high risk segment of the profession for these offences would be the surgeons. A more serious offence is Section 304A, which penalises a rash or negligent act which would not amount to culpable homicide (i.e. where there is no intention to cause death, nor knowledge that death may be caused) but would lead to death. Although the punishment is only 2 years, the resort to this offence is the greatest and would only apply when the patient dies as a direct and proximate result of the negligence of the doctor.

Consent

The basis for recognising consent to medical treatment is the individual's right to autonomy or self-determination. As stated by Cardozo J:

"Every human being of adult years and sound mind has a right to determine what shall be done with his own body; and a surgeon who performs an operation without his patient's consent commits an assault".

Consent to treatment could be express or implied by the patient's conduct. Once the patient has come to the doctor for treatment and paid the professional fee, he is said to have impliedly consented to the treatment, such a consent being valid only for examination and not for the performance of any procedure. Express consent could be oral or written.

For there to be a valid consent in case of a future legal proceeding, it is advisable to ensure that the consent is always expressed in writing. But it is pertinent to note that standard consent forms only indicate that the nature and purpose of the treatment have been explained to the patient. They are not conclusive of the fact that the patient consented to the procedure in question. In *Chatterton V. Gerson*[1] the court held that a proforma expressing consent of the patient is a valuable reminder to everyone of the need for explanation and consent. But it does not amount to a defence to an action based on trespass to the person if no explanation has been given. "The consent would be expressed in form only not in reality".[1] For the consent to be valid in law, it must be an informed consent. The patient must consent to the treatment after understanding the nature of the treatment. Before this, he must have some information about the procedure itself. This proposition of law was laid down in *Chatterton* vs *Gerson.*[1]

Without adequate consent, the doctor might face the risk of proceedings for battery in case of any complications arising from the medical procedure. Therefore, to protect himself in case of future litigation, it is important for the doctor to have a written consent form, where it should be specified that the procedure, including its risks, has been explained to the patient, and the patient has thereafter decided to go ahead with the treatment. It is advisable to get the form signed in the presence of an independent witness.

Children

The next question that needs to be addressed is what happens to the consent of a child. For this purpose, Jones[1] divides children into two categories:

- Those who have the capacity to make their own decisions about medical treatment and can give valid consent on their own, and
- Those who do not have capacity, in which case parental consent becomes necessary.

As per the Indian Majority Act, 1875[1] a person attains majority upon the completion of eighteen years of age. A person below 18 years of age is a minor.[1]

But in cases where the child lacks the relevant capacity to consent to treatment, parental consent is required unless there is an emergency.[2] As per the law laid down in Gillick, parental rights to control a child exist only for the benefit of the child and extend only so far as they extend to protecting the interests of the child. A slightly different approach was taken by the Court in the case of Re T (a minor) (wardship: medical treatment)[3] in which a child was born with a life-threatening liver defect. The doctors indicated that the child was likely to have a normal life if it underwent a liver operation, but the mother refused to give her consent. Under wardship jurisdiction, the judge granted permission for the operation in the best interests of the child, but the court of appeal held that the welfare of the child depended on the mother, who would be expected to care for him for many years. Thus, the mother's views were held to be relevant even if the doctors felt that the same was unreasonable.

In England, the court held in *Gillick* vs *West Norfolk and Wisbech Area Health Authority*[1] that if the patient is capable of understanding what is proposed, and of expressing his or her own wishes, there is no good reason for holding that he or she lacks the capacity to authorise the doctor to perform an examination or give treatment.

From this it would follow, that it is imperative to get the consent of the parents in cases such as these. An option would be to get an order from the court allowing the treatment despite lack of parental consent. Such an order would protect the interests of the doctor in case he decides to go ahead with the treatment even though the parents have indicated their views against the same.

Emergencies and Intensive Care

The law on the standard of care to be exercised by a doctor in Intensive Care is not very developed or clear. It is submitted that while there is a lack of specific case law on doctor's liability in Intensive Care, the basic principles stated above, can be applied to such situations. In an English case, *Sherlock* vs *North Birmingham Health Authority*[4] an eight month old infant who was suffering from pneumonia and myocarditis was to be transferred to the Intensive Care Unit, but there was a delay in calling the Registrar of the hospital in order to transfer him. On the way to the Intensive Care Unit, the baby suffered a cardiac arrest which resulted in permanent brain damage. On the facts of the case the court held that there was no negligence as it was established that the patient would have suffered cardiac failure even if he was transferred to intensive care earlier.

Children and Emergencies

A doctor can provide medical treatment to a child in the absence of parental consent in an emergency, based on the principle of necessity. But what happens in case parents refuse consent to a treatment that could be life-saving for the child? Will the doctor be justified in performing the treatment in the light of express prohibition?

It seems that while this proposition of law is not entirely clear, it could be argued that it is possible, in some cases, for the doctor to act in disregard of parental prohibition. Here the words of Lord Templeman in the *Gillick* case are to be noted, wherein he remarked:

"I accept that if there is no time to obtain a decision from the court, a doctor may safely carry out treatment in an emergency if the doctor believes the treatment to be vital to the survival or health of an infant and notwithstanding the opposition of a parent or the impossibility of alerting the parent before the treatment is carried out.

In such a case the doctor must have the courage of his convictions that the treatment is necessary and urgent in the interests of the patient and the court will, if necessary, approve after the event treatment which the court would have authorised in advance, even if the treatment proves to be unsuccessful."

Consumer Protection Act and the Medical Profession

Liability for doing of a wrong is inherent in law. Consumer Protection Act, 1986 is only a special means of enforcing such rights provided to the consumers of goods and services. The fact that the medical profession and the services this sector has to offer is covered within the ambit of Consumer Protection Act, is now settled.[5]

Consumer Protection Act—The Scheme

The Consumer Protection Act, 1986 was enacted in 1986 "to provide for better protection of the interests of consumers." It creates a parallel Dispute Redressal Mechanism, and provides for a time limit within which the disputes need to be adjudicated upon, which makes the remedy one of the most favored with litigants. Under the scheme of the Consumer Protection Act, 1986, as it stands today, any person who hires or avails of any services for consideration (and includes any beneficiary of such services) qualifies to be a consumer as per the definition in Section 2 (d) of the Act. In the event that the services hired or availed of by a consumer suffer from deficiency in any respect, the consumer can approach the consumer fora for redressal of his grievances, but only for remedies provided under the Act. Service under the Act would include service of any description but does not include rendering of any service free of charge or under a contract of personal service.[6] Deficiency has been defined under the Act as any fault, imperfection or shortcoming in the quality, quantity, potency, purity or standard. Clearly this is a very wide definition, and the determination of this would depend upon and differ in each case.

The negligence will have to be established by the complainant after the production of expert evidence indicating the negligence, and in the absence of such evidence the opposite party cannot be said to have been negligent in the treatment of the patient.[7]

Proceedings under the Act

Upon a consumer dispute arising, i.e. upon the filing of a complaint and its being contested in the forum, the forum/commission would proceed to settle the consumer dispute in the manner prescribed under the Act. If after the course of the proceedings, the forum is satisfied that the allegations contained in the complaint regarding the services are proved, it may order the defendant to:

a. return to the complainant, the charges paid by the complainant;
b. remove the defect in the services provided;
c. pay such amount as may be awarded as compensation to the consumer for any loss or injury suffered by the consumer due to the negligence of the opposite party.

Deficiency of Service and Negligence

It is very important to distinguish "deficiency of service" and "negligence". It is clear that as soon as there is deficiency of service, the cause of action to the consumer to approach the consumer forum would accrue. In the event that the consumer proves that there has, in fact, been a deficiency of service, he would be entitled to orders as detailed above. However, where the consumer seeks compensation under the Act, it would be imperative to determine that the defendant has been negligent in performing its duty, and only the loss caused to the consumer due to such negligence can be compensated. The causation of loss arising out of the negligent conduct of the defendant is a pre-condition for grant of compensation in terms of the Act.

Another important facet of the Consumer Protection Act, 1986 is that all complaints need to be filed within two years from the date on which the cause of action (the alleged wrong done) arises.

Safeguards

The most vital safeguard against an action under the Consumer Protection Act, 1986, or in civil liability would be to exercise the necessary degree of care, not only in discharging the duties, but also in recording the manner in which the treatment has progressed. It would be advisable to maintain files/records even for outpatients, and all documentation to be recorded therein. It is seen that the prescription that is given to the patient is normally not retained in the Hospital. It is advisable that a copy of the prescription be retained for future use, and to avoid tampering by the complainant.

It is also felt that the prescriptions/summaries that are prepared during taking of history/diagnosis/treatment be recorded in detail, and the differential diagnosis etc. also be recorded. It is sometimes impossible for a doctor to recollect the incident after long time having elapsed between the incident and the complaint, and this would only serve as a tool for refreshing of memory. It would also help the patient in analysing the course of treatment being given to him, and also enable any other medical professionals that he may consult subsequently to make informed decisions. All advice that is given to the patient or family members, like precautions that need to be taken etc. should also be noted and confirmation (in writing) taken from the family members/patient. At times it is possible that the patient suffers damage because of not following medical advice, where it becomes essential to show that such advice was, in fact, given to the patient. Detailed consent forms describing the risks of the procedures that are being undertaken should be considered with a view that the well known and most likely complications and pitfalls of various procedures are informed to the client in advance. It is also imperative to take a written consent from the patient that he has undertaken the treatment with full knowledge of the risks involved. In short the only means to avoid frivolous litigation is to be more transparent in professional dealings. While this may lead to more paperwork and reduce the professional dealing time, in the longer run the benefits of the comprehensive case histories/treatment records would deter vexatious/frivolous litigation/claims.

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2. [1957] 2 All ER 118.
3. Daborn vs Bath Tramways Motor Co. Ltd, [1946] 2 All ER 333.
4. Michael CF, Jones A. Medical Negligence, Sweet and Maxwell, London, 1991;82.
5. Chatterton vs Gerson, [1981] 1 All ER 257-65.
6. Ibid.
7. 1st All ER 1981;257.

CHAPTER 103

Useful Information and Equations in the PICU

Praveen Khilnani

1. **Alveolar air equation**

$$PAO_2 = FiO_2\ (Pb - 47) - \frac{PaCO_2}{R}$$

Alveolar arterial oxygen gradient

$$A\text{-}a(O_2) = (FiO_2\ \%\ 100) \times (Pb\text{-}47\ mm\ Hg) - (PaCO_2/0.8) - (PaO_2)$$

- PAO_2–partial pressure of alveolar oxygen
- Pb–atmospheric barometric pressure at sea level
- 47–water vapor pressure
- $PaCO_2$–partial pressure of arterial carbon dioxide
- R–respiratory quotient = 0.8

2. **Airway resistance equation**

$$\text{Pressure} = \text{Flow} \times \text{resistance}$$

$$\text{Resistance} = \frac{8\ nl}{\text{pie}\ r^4}$$

Reistance is inversely proportional to 4th power of radius.

where pie (π) = 22/7,
where r = radius,
where l = length,
where n = viscosity.

3. **Oxygen content (CaO_2)**

$CaO_2 = PaO_2 \times 0.003 + Hb(gm) \times \%\ Sat \times 1.36$

4. **Oxygen delivery (DO_2)**

$DO_2 = CI \times CaO_2 \times 10$ normal 620 (ml/min/meter sq)

5. **Oxygen consumption (VO_2)**

$VO_2 = CI \times (CaO_2 - CvO_2) \times 10$ 120-200 (ml/min/meter sq)

6. **Oxygen extraction**

$$\frac{CaO_2 - CvO_2}{CaO_2} \times 10$$

7. **Shunt equation**

$$\frac{Qs}{Qt} = \frac{CcO_2 - CaO_2}{CcO_2 - CvO_2}$$

8. **Systemic to pulmonary shunt (Qp/Qs)**

$$\frac{Qp}{Qs} = \frac{SaO_2 - SmvO_2}{SpvO_2 - SpaO_2}$$

9. **Systemic vascular resistance index (SVRI)**

$$SVRI = \frac{MAP - CVP}{CI} \times 80 \quad 800 - 1200\ dynes/sec/cm^5$$

10. **Pulmonary vascular resistance index (PVRI)**

$$PVRI = \frac{MPAP - PCWP}{CI} \times 80 \quad 20 - 120\ dynes/sec/cm^5$$

- MPAP—mean pulmonary artery pressure : 15 mm Hg (syst 25/diast10)
- PCWP—pulmonary capillary wedge pressure: 9 mm Hg (8-12)
- MAP—mean arterial pressure (syst + 2 × diastolic/3)
- SaO_2—arterial oxygen saturation
- $SmvO_2$—mixed venous oxygen saturation
- $SpvO_2$—pulmonary venous oxygen saturation
- $SpaO_2$—pulmonary arterial oxygen saturation
- CI cardiac index (cardiac output/surface area 3.2-5.2 L/msq)

- CcO_2—pulmonary capillary oxygen content
- CaO_2—arterial oxygen content
- CvO_2—venous oxygen content
- SVI stroke volume index CI × 1000/hr: 37-47 ml/beat/m^2

Pharmacokinetics

1. Concentration = dose × 1/2 life
   = Vol D × 0.69
2. Loading dose = concentration desired × Vol D
3. Clearance = rate of administration steady state concentration
   Vol D = volume of distribution
   Peak level (drug concentration) (E.g. usually one hour after gentamicin administration) if high reduce the dose. If low increase the dose.
   Trough level (drug concentration) (E.g. before the next dose usually after three doses of gentamicin given to achieve steady state) if high increase the dose interval, if low decrease the dose interval.
4. $\frac{\text{Drip rate}}{\text{concentration}} = \frac{\text{Drip rate (New)}}{\text{concentration (New)}}$

Drip Calculation

$$\frac{\text{Drug concentration}}{\text{mg/100 ml}} = \frac{6 \times \text{desired dose (mics/kg/min)}}{\text{desired fluid rate ml/hr}} \times \text{kg}$$

or

$$\frac{6 \times \text{body weight in kg}}{1 \text{ ml/hr}} = \frac{\text{mg of drug in 100 ml}}{1 \text{ mic/kg/min}}$$

Acid-base/Renal/Fluids

- 10 mm Hg PaO_2 = 0.08 unit pH
- 0.15 unit pH = 10 mEq/L HCO_3

Increase in pCO_2 by 10 mm Hg + increase HCO_3 by 1 mEq/L

Decrease in pCO_2 by 10 mm Hg =
(acute) decrease HCO_3 by 1.5 mEq/L
(chronic) decrease HCO_3 by 3 mEq/L

Serum osmolarity $= 2(\text{Na}) + \frac{\text{blood glucose}}{18} + \frac{\text{BUN}}{2.8}$

Anion gap = Na – (Cl + HCO_3)
139 – (105 + 24) = 11 (>15 abnormal)

FeNa (fractional excretion of Na) $= \frac{\text{Urine/Plasma Na}}{\text{Urine/Plasma Cr}}$

< 1 Prerenal
> 1 Renal

Renal failure index (RFI) $= \frac{\text{Urine Na}}{\text{U/P Cr}}$

< 1 Prerenal
> 1 Renal

Maintenance fluids

• 10 kg	4 ml/kg/hr
• Next 10 kg	2 ml/kg/hr
• More than 20 kg	1 ml/kg/hr
(for 20 kg child	60 ml/hr)
• Fluid bolus	20 ml/kg up to three to four times

Temperature Conversion

Degree F (Fahrenhiet) = 32 + degree centigrade (Celcius) × 9/5 (or 1.8)
So,

38°C = 38 × 9/5 + 32 = 68.5 + 32 = 100.5 F

BSA (Body surface area)

Wt (kg)	*BSA (meter sq)*
2	0.12
3	0.2
4	0.23
5	0.25
6	0.29
7	0.33
8	0.36
9	0.40
10	0.44
15	0.62
20	0.79
25	0.93
30	1.07
35	1.20
40	1.32
45	1.43
50	1.53
55	1.62
60	1.70
65	1.78
70	1.84

Biostatistics

1. $$\text{Sensitivity} = \frac{\text{True positive}}{\text{True positive} + \text{False negative}}$$

2. $$\text{Specificity} = \frac{\text{True negative}}{\text{True negative} + \text{False positive}}$$

3. Positive predictive value

$$= \frac{\text{True positive}}{\text{True positive} + \text{False positive}}$$

4. Negative predictive value

$$= \frac{\text{True negative}}{\text{True negative} + \text{False negative}}$$

5. False negative rate

$$= \frac{\text{False negative}}{\text{True positive} + \text{False negative}}$$

6. False positive rate

$$= \frac{\text{False positive}}{\text{True negative} + \text{False positive}}$$

CHAPTER

Drugs Used in the Pediatric Intensive Care Unit

Ruchi Jain, Praveen Khilnani

Generic name (Trade name)	*Dose/Route of administration*	*How supplied/Major side effects*
Acetaminophen/Paracetamol (Calpol, crocin, malidens, metacin, paracin, inj febrinil)	10-15 mg/kg q 4 h (maximum: 5 doses/24 hr)	*Drop:* 150 mg/ml *Syrup:* 125/5 ml *Tablets:* 125, 250, 500, 650 *Injection:* 150 mg/ml *Adverse event*: Hepatic necrosis
Acetazolamide (Diamox, Actamid)	*Diuretic* 5 mg/kg/day q 8 hr PO or IV *Glaucoma* 20-40 mg/kg/day q 6 hr IM or IV; 8-30 mg/kg/day q 6 hr to q 8 hr PO *Hydrocephalus in infancy* Initial: 25 mg/kg/day tid PO or IV Increment: 25 mg/kg/day (maximum: 100 mg/kg/day or 2 g/day *Seizures* 8-30 mg/kg/day q 6 hr to q 8 hr (maximum: 1 g/day) *Urine Alkalinization* 5 mg/kg repeated two to three times in a day	*Tablet:* 250 mg *Adverse events*: Metabolic acidosis, hypochloremia, hypokalemia, nausea, anorexia, drowsiness, fatigue, muscle weakness, renal calculi.
Acetylcysteine (Mucomyst)	*Acetaminophen (Paracetamol) poisoning* 140 mg/kg PO or NG, then 70 mg/kg q 4 hr for total of 18 doses beginning within 10 hr of ingestion: repeat dose if emesis occurs within 1 hr. Dilute acetylcysteine 1:4 in water, saline solution or juice for oral administration; diluted solutions should be freshly prepared and used within 1 hr. *Meconium Ileus* *Infants*: Contraindicated; Surgery is the treatment of choice *Children*: 5-30 ml administered 3-6 times in a day PO or PR or 100-200 ml by irrigation bid. *Nebulizer* 6-10 ml of 10% solution administered tid to qid	*Solutions:* 10%, 20% *Adverse events*: Stomatitis, nausea, vomiting, urticaria
Acyclovir (Acivir, Cyclovir, Herpex Zovirax)	*Herpes Simplex Virus* *Neonates*: 30-45 mg/kg/day IV q 8 hr *Children and adults*: 15 mg/kg/day IV q 8-12 hr *HSV in Immunocompromised*	*Ointment:* 5% w/w *Injection:* 250 mg/ml *Suspension:* 200 mg/5 ml, 400 mg/5 ml *Tablet:* 200 mg, 400 mg, 800 mg

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	Children and adults: 15-30 mg/kg/day IV q 8 hr Varicella zoster 1500 mg/m^2/day IV q 8 hr *Topical Use* Apply ointment 5-6 times a day	*Adverse events*: Headache, dizziness, rash, bone marrow suppression.
Adenosine (Adenoject, Tachyban)	*Neonates and children*: 0.05 mg/kg IV push, then increase bolus doses by 0.05 mg/kg every 2 min until a clinical response occurs or a maximum dose of either 0.25 mg/kg or 12 mg is achieved. *Adults*: 6 mg IV push, if no response in 2 min, give 12 mg IV push. May repeat 12 mg IV bolus if needed.	*Injection:* 30 mg/ml. *Adverse events*: Heart block, flushing, palpitations, bradycardia, hypotension, dyspnea, headache, dizziness, nausea.
Adrenocorticotropic hormone	*Children*: Inflammation or immunosuppression: 1.6 units/kg/day or 50 units/m^2 divided every 6-8 hr; IM (gel): 0.8 units/kg/day divided every 12-24 hr. *Infantile spasms*: 5-160 units/kg/day has been used for 1 wk-12 mo as IM gel *Adults*: *Acute exacerbations of Multiple sclerosis:* 80-120 units/day for 2-3 wk.	*Aqueous injection:* 25, 40 U/vial Gel for injection: 40, 80 U/ml.
Albumin Human (Albudac, Albupan, Albumin)	*Neonates*: 0.5-1 g/kg/dose (max 1 g/kg/day). *Infants and children*: 0.5-1 g/kg/dose (max 6 g/kg/day). *Adults*: 25 g/dose (max 250 g/day).	*Solution*: 5%, 20% *Suspension*: 10, 50, 100 ml *Adverse events*: Precipitation of heart failure, hypertension, immune reactions.
Amikacin sulfate (Aerobact, Amcin, Amexel, Ambiotic)	*Neonates*: Postnatal age <7 days: 1200-2000 g: 7.5 mg/kg q 12-18 hr; > 2000 g: 10 mg/kg q12 hr; Postnatal age > 7 days: 1200-2000 g: 7.5 mg/kg q 8-12 hr, > 2000 g: 10 mg/kg q 8 hr. *Children*: 15-25 mg/kg/day divided q 8-12hr. *Adult*: 15 mg/kg/day divided q 8-12 hr.	*Injections:* 50, 100, 250, 500 mg/ml *Adverse events*: ototoxicity, nephrotoxicity.
Aminocaproic Acid (Amicar, hamostat)	*Children*: load 100-200 mg/kg, maintenance 100 mg/kg every 6 hr or 33.3 mg/kg/hr continuous infusion. *Traumatic hyphema:* 100 mg/kg every 4 hr (max 30 g/day). *Adults*: load 5 g over 1 hr, then 1-1.25 g/hr until bleeding stops.	*Injection:* 250 mg/ml *Tablet:* 500 mg *Syrup:* 250 mg/ml *Adverse events*: Hypotension, bradycardia, arrhythmias, nasal congestion, headache.
Aminophylline	*Neonates*: Loading dose 6 mg/kg IV or PO. Maintenance dose: 2.5-3 mg/kg/dose q 12 hr IV or PO. *Children*: 6 wk-6 mo: 0.5 mg/kg/hr. 6 mo-1 yr: 0.7 mg/kg/hr 1-9 yr: 1 mg/kg/hr 9-12 yr: 0.9 mg/kg/hr 12 yr-adult: 0.7 mg/kg/hr *Therapeutic level:* *Asthma:* 10-20 µg/ml *Neonatal apnea:* 6-12 µg/ml	*Tablets:* 100 mg *Injection ampoule:* 250 mg/ml. *Adverse events:* Nausea, vomiting, CNS irritability, agitation, tachyarrhythmias and tachycardia.
Amiodarone (Aldarone, Amiodar, panaron)	Oral dose: *Infants and children:* < 1 yr: 600-800 mg/2.73 m^2/day in two divided doses. > 1 yr: 10-15 mg/kg/day in two divided doses. *Adults*: 800 mg/kg/day in two divided doses. Cut all doses to half, i.e. one dose per day after 1-4 wk of treatment or arrhythmias are controlled. IV dose: *Infants and children*: load 5 mg/kg over 1 hr, then continuous infusion of 5-15 µg/kg/min.	*Tablets:* 100, 200 mg. *Injection:* 3 ml *Adverse events*: Proarrhythmia, fatigue, nightmares, hypothyroidism, hyperglycemia, photosensitivity, hypersensitivity pnemonitis, photophobia, elevated triglycerides, skin rash, liver toxicity.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	Adults: 150 mg over 10 min, then 0.5 mg/min.	
Ammonium Chloride	*Children*: 75 mg/kg/day IV divided q 6 hr (max daily dose: 6 g). *Adults*: 1.5 g/dose IV q 6 hr.	*Adverse events*: Hyperchloremia, hyperammonemia, hyperkalemia.
Amoxicillin (Amoxil, Amoxybid, Damoxy, Hipen, Novamox)	*Children*: 20-50 mg/kg/day PO divided q 8-12 hr. Higher dose 80-90 mg/kg/day for *otitis media*. *Adult*: 250 mg-500 mg PO q 8-12 hr. *Uncomplicated gonorrhea*: 3 g + 1g probenicid.	*Capsules:* 125, 250, 500 mg. *Syrup:* 125/5 ml *Kid tablet:* 125 mg. *Adverse events*: Skin rash, diarrhoea, abdominal cramping.
Amoxicillin and Potassium clavulanate (Augmentin, Novaclav, Clavum)	*Neonates*: 30 mg/kg/day divide q 8-12 hr. *Children*: 20-45 mg/kg/day divided q 8-12 hr. Higher dose 80-90 mg/kg/day for *otitis media*.	*Tablets:* 375, 625 mg *Syrup:* 125, 200 mg of amoxycillin/5 ml *Injections:* 300, 600, 1200 mg. *Adverse events*: diarrhoea, skin rash.
Amphotericin B		
(a) Conventional	Start with 0.25 mg/kg q 24 hr iv and increase by 0.25 mg/kg/day to maximum of 1 mg/kg/day	Injection-50 mg/vial Adverse events: Hypotension flushing nephrotoxicity, hypokalemia, hypomagnesemia
(b) Lipid Complex	Start with 1 mg/kg q 24 hr iv and increase by 1 mg/kg/day to maximum of 5 mg/kg/day q 24 hr	Injection-10 mg, 50mg/vial
(c) Liposomal	Start with 1 mg/kg q 24 hr iv and increase by 1 mg/kg/day to maximum of 5 mg/kg/day q 24 hr	
Amirinone (Amicor)	*Adults*: Initial loading dose: 0.75 mg/kg. *Maintenance infusion:* 5-10 µg/kg/min. Max daily dose 10 mg/kg.	*Injection:* 100 mg. *Adverse effects*: Arrhythmia, GI disturbances, myositis, thrombocytopenia, hypersensitivity.
Artemether (Paluther, larither)	3.2 mg/kg IM on day 1, then 1.6 mg/kg/day for 4 days.	*Capsule:* 40 mg. *Injection:* 80 mg/ml. *Adverse effects*: Increase in liver enzymes.
Atenolol (Aten, betacard, tenolol)	*Children*: 0.8-1.5 mg/kg/day (max 2 mg/kg/day). *Adults*: 25-200 mg/day oral, 5 mg IV over 5 min.	*Tablets:* 50, 100 mg. *Adverse events*: Bradycardia, lethargy, headache, constipation, wheezing, dyspnea.
Atracurium besylate (Tracrium)	< 2 *yr*: 0.3-0.4 mg/kg as needed. > 2 *yr to adult*: 0.4-0.5 mg/kg then 1 mg/kg 20-45 min after each initial block to maintain effect. Continuous infusion: 0.4-0.8 mg/kg/hr.	*Injection:* 10 mg/ml. *Adverse events*: Respiratory depression, bronchospasm, hypersensitivity.
Atropine sulphate	*Neonates and children*: < 5 kg: 0.2 mg/kg 30 min preop then every 4-6 hr. > 5 kg: 0.1-0.2 mg/kg/dose (max 0.4 mg/dose). *Adults*: 0.4-0.6 mg IV or SC 30 min preop. Treatment of sinus bradycardia *Neonates and children*: 0.02 mg/kg (min dose 0.1 mg); IV or intratracheal (max dose 0.5 mg); may repeat 5 min later, one time. *Adults*: 0.5-1 mg every 5 min (max total dose 2 mg). Antidote to organophosphate poisoning 0.02-0.05 mg/kg every 10-20 min until atropine effect (tachycardia, mydriasis, fever), then every 1-4 hr for at least 24 hr.	*Injection:* 0.6 mg/ml. *Ointment:* 1% *Eye drops:* 1% *Adverse events*: Tachycardia, palpitations, delirium, ataxia, dry hot skin, tremor, impaired vision.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Azithromycin	Adults: 500 mg PO OD Children >6 months 10 mg/kg q 24 hr	Oral-200 mg, 100 mg/5 ml Adverse effects: Nausea, abdominal Discomfort, rash, photosensitivity.
Aztreonam	*Neonates*: Postnatal age < 7 days: < 2000 g: 60 mg/kg/day q 12 hr; > 2000 g: 90 mg/kg/day q 8 hr; Postnatal age> 7 days: < 1200 g 60 mg/kg/day divided q 12 hr; 1200-2000 g: 90 mg/kg/day divided q 8 hr, > 2000 g: 10 mg/kg q 8 hr. *Children*: 90-120 mg/kg/day divided q 6-8 hr. *Cystic fibrosis* up to 200 mg/kg/day. Adult: 1-2 g q 8-12 hr. (max 8/day).	
Bicarbonate sodium	*Cardiac arrest* *Infants and children*: 0.5-1.0 mEq/kg; repeat every 10 min or as indicated by arterial blood gas values. *Adults* Initial: 1 mEq/kg Maintenace: 0.5 mEq/kg every 10 min or as indicated by arterial blood gas values (bicarbonate should only be given after adequate ventilation has been established and effective cardiac compressions have been provided); routine use of bicarbonate in patients in cardiac arrest is not recommended. *Metabolic acidosis* Dose requirement (in mEq bicarbonate) for complete correction can be approximated using following formulas: 0.3 × weight (kg) × base deficit (mEq/ml) 0.5 × weight (kg) × (Serum HCO-3 - 24 mEq/ml) *Chronic renal failure* 1-3 mEq/kg/24 hr Renal tubular acidosis *Distil* *Infants*: 2-3 mEq/kg/24 hr *Adults*: 1 mEq/kg/24 hr *Proximal* *Initial:* 5-10 mEq/kg/24 hr *Maintenance:* Increase dose as necessary to maintain serum bicarbonate level in normal range.	*Injection* 7.5%: 1 mEq/ml *Adverse events*: Alkalosis, intraventricular hemorrhage, hypernatremia, bradycardia. Clots with calcium infusion.
Bisacodyl	*Children* < 2 yr: 5 mg rectal suppository. > 2 yr: 10 mg rectal suppository. > 6 yr: 5-10 mg oral at bedtime or before breakfast. *Adults:* 5-30 mg oral dose, 10 mg rectal suppository.	*Adverse events:* Fluid and electrolyte imbalance, abdominal cramps.
Bumetanide (Bumet)	*Neonates:* 0.01-0.05 mg/kg/dose every 24-48 hr. *Infants and children:* 0.015-0.1 mg/kg/dose every 6-24 hr (max 10 mg/day). *Adults:* 0.5-2 mg/dose (max 10 mg/day).	*Tablet:* 1 mg. *Adverse events*: Electrolyte depletion, dehydration.
Calciferol, 25-hydroxycholecalciferol	*Infants:* 5-7 µg/kg/day. *Children and adults:* 20-100 µg/kg daily or every other day titrated to obtain normal serum calcium and phosphate levels.	*Capsules* *Adverse events*: Hypercalcemia, Vitamin D toxicity.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side-effects
Calcitriol, 1, 25-dihydroxycholecalciferol	*Premature infants:* 0.05 µg/kg/day IV or 1 µg/day orally. *Children:* 0.01-0.08 µg/kg/day. *Adults:* 0.25-1 µg/day.	*Adverse events*: Hypercalcemia, Vitamin D toxicity.
Calcium salts Ca carbonate: 400 mg = 20mEq Ca Gluconate:90mg = 4.5 mEq (Calcal, calcidon, Calcium sandoz, Mecalvit, Ossopan, Osteocalcium)	*Hypocalcemic Tetany* *Neonates:* 2.4 mEq/kg/day in divided doses (if due to citrated blood tranfusion give 0.45 mEq per 100 ml transfused blood). *Infants and children:* 10 mg/kg over 5-10 min (may repeat in 6-8 hr) followed by infusion of max dose of 200 mg/kg/day. *Adults:* 4.5-16 mEq repeated until response *Cardiac Arrest* (only if hypocalcemia) *Infants and children:* 20 mg/kg IV and may repeat in 10 min. *Adults:* 2-4 mg/kg repeated every 10 min as needed. **Prevention of Calcium Depletion** *Children:* < 6 mo: 400 mg/day. 6-12 mo: 600 mg/day. 1-5 yr: 800 mg/day. 6-10 yr: 800-1200 mg/day. > 10 yr and adult: 1000-1500 mg/day.	*Adverse events:* Constipation, hypercalcemia, milk-alkali syndrome, calcium burns with extravasation, bradycardia.
Captopril (Aceten, Captopril)	*Premature newborns:* 0.01 mg/kg every 8-12 hr. *Neonates:* Initial 0.05-0.1 mg/kg/dose every 8-24 hr and titrate upward to response (max dose 0.5 mg/kg/dose every 6-24 hr). *Infants:* Initial 0.15-0.3 mg/kg/dose; and titrate upward (max 6 mg/kg/day divided into 1-4 divided doses). *Children:* Initial 0.3-0.5 mg/kg/dose and titrate upward (max 6 mg/kg/day divided into 2-4 divided doses). *Older children:* Initial 6.25-12.5 mg/kg/dose every 12-24 hr and then titrate (max 6 mg/kg/day divided into 2-4 divided doses). *Adolescents and adults:* Initial 12.5-25 mg/dose and titrate (max 450 mg/day).	*Tablets:* 12.5, 25 mg. *Adverse events*: Cough, angioedema, oliguria, hyperkalemia.
Carbamazepine (Mazetol, Tegretal)	*Children:* < 6 yr: Initial 5 mg/kg/day in 2-4 divided doses; may increase every 5-7 days by 5 mg/kg based on effect or toxicity and serum concentration. 6-12 yr: Initial 10 mg/kg/day in 2-4 divided doses; increase by 100 mg or 5 mg/kg/day at weekly intervals until therapeutic levels are achieved (usual dose 800-1000 mg/day). *Adults:* Initial 200 mg twice daily; increase by 200 mg at weekly intervals until therapeutic levels are achieved (usual dose 1.6 to 2.4 g/day in 3-4 divided doses).	*Tablets:* 100, 200, 400 mg *Suspension:* 100 mg/5 ml. *Adverse events:* Sedation, dizziness, fatigue, blurred vision, nystagmus, marrow suppression, hepatitis, hypersensitivity reactions.
Caspofungin (Cancidas)	For aspergillus, neutropenic with candida patients *Adults:* 70 mg loading then 50 mg once a day. *Pediatrics:* 50 mg/m^2/day	Less toxic than amphoterecin. Hepatotoxicity, rash
Cefazolin (Azolin, Orizolin)	*Neonates:* Postnatal age ≤7 days 40 mg/kg/day divided q 12 h; >7 days 40-60 mg/kg/day divided q 8 h. *Children:* 50-100 mg/kg/day divided q 8 h. *Adults:* 0.5-2 g q 8 h (max dose 12 g/day).	*Injections:* 250, 500 mg, 1 gm. *Adverse events*: Rash, eosinophilia.
Cefixime (Cefspan, Biotax, Sefxim, Taxim-O)	*Children:* 8 mg/kg/day divided q 12 h. *Adults:* 400 mg/day divided q 12-24 h.	*Tablets:* 100, 200, 400 mg *Oral suspension:* 50, 100 mg/5 ml. *Adverse events*: Rash, eosinophilia.
Cefoperazone (Magnamycin, Zefex)	*Neonates:* 100 mg/kg/day divided q 12 h. *Children:* 100-150 mg/kg/day divide q 8-12 h. *Adults:* 2-4 g/day q 8-12 h (max 12 g/day).	*Injections:* 250, 500 mg, 1 gm/vial. *Adverse events*: Disul firam like reaction with alcohol

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Cefotaxime (Biotax, Omnatax, Taxim)	*Neonates:* Postnatal age ≤ 7 days 100 mg/kg/day divided q 12 h > 7 days < 1200 g 100 mg/kg/day divide q 12 h, >1200 g 150 mg/kg/day divided q 8 h. *Children:* 150 mg/kg/day divided q 6-8 h (meningitis 200 mg/kg/day divided q 6-8 h). *Adults:* 1-2 g q 8-12 h (max 12 g/day).	*Injections:* 125, 250, 500, 1000 mg/vial. *Adverse events:* Rash, eosinophilia.
Cefpodoxime proxetil (cefoprox, monocef-O)	*Children:* 10 mg/kg/day PO divided q 12 h. *Adults:* 200-800 mg/day PO divided q 12 h (max dose 800 mg/day). Uncomplicated gonorrhea 200 mg PO single dose therapy.	*Tablets:* 100, 200 mg *Syrup:* 50, 100 mg/5 ml. *Capsule:* 200 mg. *Adverse reactions:* Rash, eosinophilia.
Ceftazidime (Fortum)	*Neonates:* Postnatal age ≤ 7 days 100 mg/kg/day divided q 12 h; >7 days < 1200 g 100 mg/kg/day divide q 12 h, >1200 g 150 mg/kg/day divided q 8 h. *Children:* 150 mg/kg/day divided q 8 h (meningitis 150 mg/kg/day divided q 6-8 h). *Adults:* 1-2 g q 8-12 h (max 8-12 g/day).	*Injections:* 250, 500, 1000 gm/vial. *Adverse events:* Rash, eosinophilia.
Ceftriaxone (Monocef, Monotax)	*Neonates:* 50-75 mg/kg q 24 h. *Children:* 50-75 mg/kg q 24 h (meningitis 75 mg/kg/dose 1 then 80-100 mg/kg/day divided q 12-24 h). *Adults:* 1-2 g q24h (max dose 4 g/day).	*Injections:* 250, 500, 1000 gm/vial. *Adverse events:* Rash, eosinophilia.
Cefuroxime (Cefoxim, Ceftum, Zocef)	*Neonates:* 40-100 mg/kg/day PO divided q 12 h. *Children:* 200-240 mg/kg/day divided q 8 h; oral 20-30 mg/kg/day divided q 8 h. *Adults:* 750-1500 mg q 8 h (max dose 6 g/day).	*Tablets:* 125, 250, 500 mg *Susp:* 125/5 ml *Injection:* 250, 750, 1500 mg/vial. *Adverse events:* Rash, eosinophilia.
Ceftibuten (Procadax)	*Children:* 9 mg/kg qd; max 400 mg/day. *Adults:* 400 mg qd.	*Capsule:* 400 mg. *Suspension* *Adverse events:* Nausea, diarrhoea, serum sickness
Cefpirome (Cefrom)	*Adults:* 1-2 g q 12 h.	*Injection:* 1 gm/vial. *Adverse events:* Nausea, vomiting, pseudomembranous colitis, increase in liver enzymes.
Charcoal Activated	*Children and adults:* 1-2 g/kg or 5-10 times the weight of ingested poison (limit sorbitol to 1-2 times daily); may repeat doses every 2-6 hr.	*Adverse events:* Constipation, black stools.
Chloral Hydrate	*Neonates:* 25 mg/kg/dose. *Infants and children:* 25-100 mg/kg/dose. *Adult:* 250-1000 mg/dose. Doses may be repeated every 6-8 hr. Lower end doses cause sedation and higher end doses cause hypnosis.	*Adverse events:* Hepatic toxicity, bilirubin displacement in neonates.
Chloroquine (Lariago, mosquin)	*Malarial prophylaxis* *Child:* 5 mg/kg/wk (max dose 300 mg) *Adult:* 300 mg/wk. *Acute malaria treatment* *Child:* 10 mg/kg PO initial dose; 5 mg/kg 6 hr later then 5 mg/kg once daily for 2 days. IM 5 mg/kg initial dose, 5 mg/kg 6 hr later (max IM dose 10 mg/kg/24 hr). *Adult:* 600 mg initially, 300 mg 6 hr later then 300 mg once daily for 2 days. *Extraintestinal amebiasis* *Child:* 10 mg/kg daily for 2-3 wk (max daily dose 300 mg). *Adult:* 600 mg once daily for 2 days then 300 mg once daily for 2-3 wk.	*Tablets:* 250, 500 mg. *Syrup:* 160 mg/10 ml. *Injections:* 40 mg/ml, 64.5 mg/ml. *Adverse events:* Hypotension, headache, psychotic episodes, rash, peripheral neuropathy, blood dyscrasias, retinopathy, tinnitus.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Chlorothiazide	Neonates and infants < 6 mo: oral 20-40 mg/kg/day divided every 12 hr; IV:2-8 mg/kg/day divided every 12hr. Infants > 6 mo and children: oral: 20 mg/kg/day in 2 divided doses; IV; 4 mg/kg/day. *Adults:* oral: 500 mg-2 g/day in 1-2 doses; IV: 500-1000 mg/day.	*Adverse events*: Hypochloremic alkalosis, hyperglycemia, hyperlipidemia, prerenal azotemia, hyperuricemia, hypercalcemia, leukopenia.
Chlorpheniramine (Cadistin, polaramine)	*Children:* 0.35 mg/kg/day q 4 h to q 6 h (maximum: 12 mg/day) *Adults:* 4 mg q 4 h to q 6 h (maximum: 24 mg/24 hr) *Alternate dosing method* 2-6 yr: 1 mg q 4 h to q 6 h 6 yr to adults: 2 mg q 4 h to q 6 h (maximum: 12 mg/24 hr) Anaphylaxis: 0.0875 mg/kg up to 20 mg/dose IV Sustained release capsules or tablets *Children:* 0.2 mg/kg/day q 12 h (maximum: 8-12 mg/day) *Adults:* 8-12 mg q 8 h to q 12 h	*Tablets:* 2, 4, 6 mg. *Syrups:* 0.5 mg, 1 mg/5 ml. *Adverse events*: Drowsiness, excitation, dry mouth, blurred vision
Cholestyramine (Quenstran)	*Children:* 240 mg/kg/day tid; give as slurry in water, juice. *Adults:* 4g tid	*Powder:* 4 g satchet. *Tins:* 378 g. *Adverse events*: Hyperchloremic acidosis, constipation, malabsorption of fat soluble vitamins.
Chorionic gonadotropin	*Cryptorchidism:* 1000-2000 U/m^2 three times a week for 3 weeks (efficacy of this treatment is controversial; this is one of many similar dosage regimens)	*Adverse events*: Depression, tiredness, precocious puberty.
Chromium	0.2-0.4 μg/kg/day	
Ciprofloxacin (Cifran, ciplox)	*Children:* 15-30 mg/kg/day divided q 12 h. Cystic fibrosis 20-40 mg/kg/day divided q 8-12 h. *Adults:* 250-750 PO q 12 h; IV 200-400 mg q 12 h (max dose 1.5 g/day).	*Tablets:* 100, 250, 500, 750 mg. *Injection:* 100 mg/50 ml. *Adverse events*: Tendonitis, cartilage necrosis, crystalluria, photosensitivity, confusion, dizziness.
Citrate mixtures, oral	*Children:* 5-15 ml q 6 h to q 8 h PO or 2-3 mEq/kg/day q 6 h to q 8 h *Adults:* 15-30 ml PO q 6 h to q 8 h; dilute dose in water Chilling may enhance palatability.	*Adverse events*: Hypernatremia, hyperkalemia, metabolic acidosis.
Clarithomycin	15 mg/kg PO q24 hr	Nausea, vomiting, diarrhea abdominal pain
Clindamycin (Dalcap, dalacin)	*Neonates:* Postnatal age ≤ 7 days < 2000 g 10 mg/kg/day divided q 12 h; >2000 g 15 mg/kg/day divided q 8 hr; >7 days < 1200 g 10 mg/kg/day divided q 12 h; 1200-2000 g 15 mg/kg/day divided q 8 h; >2000 g 20 mg/kg/day divided q 8 h. *Children:* 10-40 mg/kg/day divided q 6-8 h. *Adults:* 150-600 mg q 6-8 h (max 2 (PO)-5 g (IM, IV)/day).	*Capsules:* 150, 300 mg *Injection:* 150 mg/ml. *Adverse events*: Diarrhea, nausea, pseudomembranous colitis, rash.
Clobazam (Frisium, lobazam)	0.1 mg/kg/day initial dose. Usual maintenance dose 0.3-1 mg/kg/day q 12 h/qhs.	*Tablets:* 5, 10, 20 mg. *Adverse effects:* Sedation, dizziness, depression, aggression.
Clonazepam (Clonotril, rivotril, lonazep)	*Children*: 0.01-0.03 mg/kg/day in 2-3 divided doses (max 250 mg/day). *Adults*: initial dose 0.1 mg twice daily; then 0.2-2.4 mg/day in 2-4 divided doses.	*Tablets:* 0.5, 2 mg. *Adverse events*: Tachycardia, chest pain, drowsiness, physical and psychology dependence.
Clonidine (Arkamin, catapres)	*Neonates:* Narcotic withdrawal: 1 μg/kg every 6-8 hr to start and may titrate to targeted abstinence score (max 2 μg/kg/dose every 4 hr).	*Tablets:* 100, 150 μg. *Injection:* 150 μg/ml. *Adverse events*: Drowsiness, dizziness, dry mouth, constipation, hypotension.

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Generic name (Trade name)	*Dose/Route of administration*	*How supplied/Major side effects*
	Children: *Attention Deficit Disorder:* Initial 0.05 mg/day, increase every 3-7 days by 0.05 mg/day given in 3-4 divided doses to response (max 0.4 mg/day) *Hypertension:* 5-10 µg/kg/day in 2-4 divided doses (max 0.9 mg/day). *Clonidine tolerance test for growth hormone release:* 4 µg/kg × 1 dose. *Adults*: hypertension oral: 0.2-2.4 mg/day in 2-4 doses titrated to response; transdermal: 0.1-0.3 mg/day titrated to effect.	
Clotrimazole (Canesten, candid-V gel, fungistat-V)	*Children and adults*: 1 troche dissolved 5-6 times daily. Vaginal cream/tablet 100-200 mg qhs. Topical cream: apply twice daily.	*Vaginal tablets:* 100, 200, 500 mg. Gel with applicator. *Adverse events*: Nausea, skin irritation.
Cloxacillin (Klox, novaclox)	*Children*: 50-100 mg/kg/day q 6 h. *Adults*: 250-500 mg q 6 h (max dose 4 g/day).	*Capsules:* 250, 500 mg. *Kid tablet:* 125 mg. *Syrup:* 125 mg/5 ml *Injections:* 250, 500 mg/vial. *Adverse events*: Rash, eosinophilia.
Co-Trimoxazole, trimethoprim-sulfamethazole (Sepmax, septran)	*Children*: 6-20 mg TMP/kg/day divided q 12 h. *Pnemocystitis:* 15-20 mg TMP/kg/day divided q 12 h. *Pnemocystitis prophylaxis:* 5 mg TMP/kg/day or 3 times/wk. *Adults:* 160 mg TMP q 12 h.	*Tablets:* 80 + 400, 160 + 800 mg. *Syrup:* 40 + 200 mg/5 ml. *Adverse events*: Rash, steven-johnson syndrome, leukopenia, nausea.
Codeine (Codin linctus)	*Analgesic* *Children:* 0.5-1.0 mg/kg q 4 h to q 6 h *Adults*: 15-60 mg q 4 h to q 6 h *Antitussive* *Children*: 0.25-0.5 mg/kg q 4 h (maximum dose 30 mg/24 hr) *Adults*: 15-30 mg q 4 h to q 6 h	*Injection:* 10 mg/ml, 15 mg/ml. *Adverse events*: Drowsiness, nausea, constipation, anorexia.
Colistin	IV infusion 16,666-25000 units/kg q 8 hrly	Injection 500,000 and 1 million units/vial
Cortisone Acetate (Cortin, cortelan, cortone)	Physiologic replacement: 0.25-0.35 mg/kg/day or 12-15 mg/m^2/day qd IM; 0.5-0.75 mg/kg/day or 20-25 mg/m^2/day qd PO Anti-inflammatory or immunosuppressive: 1-5 mg/kg/day or 30-150 mg/m^2/day q 12 h to 24 hr IM; 2.5-10 mg/kg/day or 75-300 mg/m^2/day q 6 h to q 8 h PO. *Stress:* 2-4 times physiologic replacement.	*Injections:* 25, 50 mg/ml. *Tablets:* 5, 25 mg. *Adverse events*: Insomnia, nervousness, pseudotumor cerebri headache, increased appetite, peptic ulcer, hypertension, cataracts, glaucoma, hypokalemia, diabetes mellitus.
Cromolyn sodium (Cromal, Ifiral)	Inhalant (via spinhaler): Children > 5 yr and adults: 20 mg q 6 h. *Nebulization:* Children > 2 yr and adults: 20 mg q 6 h to q 8 h. *Nasal:* One spray to each nostril tid to qid. *Ophthalmic:* 1-2 drops OU q 4 h to q 6 h. Aerosol inhaler: 2 puffs qid.	*Eye drop:* 2% *Adverse events:* Hoarseness, coughing.
Crotamiton (Crotorax)	Massage into skin of whole body from chin down with particular attention to folds and creases; reapply 24 hour later; cleansing bath should be taken 48 hour after last application	*Cream:* 10%. *Lotion:* 60 ml *Adverse events*: Local irritation.
Cyanocobalamin (vitamin B_{12})	Deficiency Haematologic signs only: 10-50 µg/day IM or SC for 5-10 days, then maintenance.	*Adverse events:* neuropsychiatric problems.

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Generic name (Trade name)	*Dose/Route of administration*	*How supplied/Major side effects*
	Neurologic signs or symptoms: 100 µg/day IM or SC for 10-15 days; total dose of 1-1.5 mg then once or twice weekly for several months; may taper to 250-1000 µg monthly by 1 yr. *Maintenance* *After treatment of deficiency:* 100-150 µg IM every 2-4 wk *Vegetarians:* 1-25 µg/day PO qd. *Diagnostic trial:* 1 µg/day IM for 10 days.	
Cyclosporin (Immusol, Sandimmun neoral)	*Children and adults*: IV: initial 5-6 mg/kg/dose started 4-12 hr prior to organ transplant; maintenance; 2-10 mg/kg/day divided q 8-12 h. *Oral:* *Initial:* 14-18 mg/kg/dose started 4-12 hr prior to transplant. *Maintenance:* 5-15 mg/kg/day divided every 12-24 hr, usually tapered to 3-10 mg/kg/day.	*Capsules:* 10, 25, 50, 100 mg *Injection:* 100 mg/ml. *Adverse effects:* Hypertension, hirsutism, nephrotoxicity, gingival hypertrophy, GI discomfort, seizure.
Dantrolene sodium	*Chronic spasticity* *Children* *Initial:* 0.5 mg/kg PO bid. *Increment:* Every 4-7 days increase frequency to tid, then doses by 0.5 mg/kg (maximum: 3 mg/kg PO bid/tid/qid or 100 mg/day). *Adults* *Initial:* 25 mg PO qd. *Increment:* Every 4-7 days increasing frequency to tid, then to qid; then increase dose by 25 mg (maximum: 100 mg PO bid or qid or 400 mg/day); if no benefits are evident within 45 days, discontinue treatment. *Malignant Hyperthermia* *Crisis:* 1 mg/kg by rapid IV infusion repeated immediately until signs of malignant hyperthermia resolve upto a total dose of 10 mg/kg Post-crisis 4-8 mg/kg day IV or PO qid for 1-3 days. Preoperative prophylaxis: 4-8 mg/kg/day qid for 1-2 days before surgery with last dose given 3-4 hr before surgery.	*Adverse events*: Drowsiness, fatigue, dizziness, blurred vision, seizures, diarrhoea, pleural effusion with pericarditis, hepatitis.
Deferoxamine (Desferal)	*Deferoxamine challenge test:* 1 gm IM; presence of salmon pink color to urine indicates significant ingestion of iron. Acute Iron poisoning IM (use only if IV access if unavailable) *Children*: 50 mg/kg q 6 h until urine no longer salmon pink colored. *Adults*: 1-2 g q 6 h until urine no longer salmon pink colored. IV *Children*: 15 mg/kg/hr by continuous infusion- do not exceed this rate. *Adults:* 1 g × 1, then 0.5 g q 4 h × 2 and q 4 h to q 12 h until urine no longer salmon pink colored–do not exceed infusion rate of 15 mg/kg/hr.	*Injection:* 500 mg/vial *Adverse events*: Flushing, hypotension, tachycardia, fever, hearing loss, blurred vision, cataracts.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	Chronic iron overload: 20-50 mg/kg/day infused SC over 8 hr.	
Desmopressin (Desmospray, minirin)	*Diabetes insipidus* Intranasal *Children* (3 mo-12 yr): 5-30 µg/day qd or bid. *Adults:* 10-40 µg/day bid or tid. IV or SC *Adults*: 2-4 µg/day bid. *Hemophilia A and von Willebrand's disease* *Intranasal:* 2-4 µg/kg. IV: 0.2-0.4 µg/kg or 10 µg/m^2/dose IV over 15-30 min (repeated doses < 48 hr apart may lead to tachyphylaxis). *Nocturnal enuresis* > 8 yr: 20 µg intranasally qhs; may increase to 40 µg qhs if patient does not respond. Some patients may respond to 10 µg; adjustment to lower dose may be tried if patient responded to 20 µg.	*Injection:* 4 µg/ml. *Nasal spray:* 10 µg/spray. *Adverse events:* Flushing, headache, dizziness, hypertension, hyponatremia, water intoxication.
Dexamethasone (Decadron, wymesone, dexona)	*Airway edema:* 0.25-0.5 mg/kg q 6 h as needed for croup or beginning 24 hr before planned extubation, then q 6 h × 4-6 doses. *Anti-inflammatory or immunosuppressive* *Children*: 0.03-0.15 mg/kg/day or 1-5 mg/m^2/day q 6 h to q 12 h. *Adults*: 0.75-0.9 mg/day q 6 hr to q 12 h. *Cerebral edema* *Load:* 1.5 mg/kg × 1 (adult: 10 mg) *Maintenance:* 0.2-0.5 mg/kg/day q 6 h × 5 days; then taper over 5 days and discontinue (adult: 4 mg q 6 h). *Croup:* 0.6 mg/kg IM/IV × 1 at admission. *Meningitis:* 0.15 mg/kg/dose IV q 6 h × 4 days. *Antiemetic:* 4-8 mg/m^2 IV loading dose; then 2-4 mg/m^2 IV q 6 h. *Ophthalmic inflammation:* Apply tid to qid.	*Injection:* 4 mg/ml. *Tablet:* 0.5 mg *Adverse events*: Insomnia, nervousness, hypertension, hyperglycemia, cataracts, adrenal suppression, poor growth.
Dextromethorphan (Lastuss-LA, suppressa)	*Children*: 1-2 mg/kg/day tid to qid (sustained action dose bid) *Adults*: 60-120 mg/day tid to qid.	*Syrup:* 10 mg/5 ml, 30 mg/5 ml *Adverse events*: GI upset, Respiratory depression.
Diazepam (Valium, calmpose, placidox)	*Sedative/muscle relaxant* *Children*: 0.04-0.2 mg/kg IM or IV q 2 h to q 4 h (maximum: 0.6 mg/kg/8 hr); 0.12-0.8 mg/kg/day PO q 6 h to q 8 h. *Adults*: 2-10 mg IM or IV q 3 h to q 4 h PRN; 2-10 PO q 6 h to q 8 h PRN. *Status epilepticus* *Neonates*: 0.1-0.3 mg/kg IV every 15-30 min × 2-3 doses *Children* 1 mo-5 yr: 0.2-0.5 mg/kg IV every 15-30 min × 2-3 doses (maximum total dose: 5 mg) *Children > 5 yr* 0.2-0.5 mg/kg IV every 15-30 min × 2-3 doses (maximum total dose: 10 mg) *Adults*: 5-10 mg IV every 10-15 min × 2-3 doses (maximum total dose: 30 mg)	*Injection:* 10 mg/2 ml. *Oral solution:* 2 mg/5 ml. *Tablets:* 2, 5, 10 mg *Rectal:* 2 mg/ml. *Adverse events*: Hypotension, bradycardia, cardiac arrest, constipation, diarrhea, physical and psychological dependence, diplopia.
Diazoxide (Eudemine, hyperstat)	*Hypertensive crisis* *Children*: 3-5 mg/kg IV as bolus injection given as fast as	*Injection:* 15 mg/ml. *Tablet:* 15 mg.

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Generic name (Trade name)	*Dose/Route of administration*	*How supplied/Major side effects*
	possible; may repeat in 30 min and q 3 h to q 10 h PRN *Adults*: 1-3 mg/kg (maximum: 150 mg/dose; repeat in 5-15 min PRN, then q 4 h to q 24 h). Hyperinsulinemic hypoglycemia *Newborns and infants*: 8-15 mg/kg/day q 8 h to q 12 h. *Children and adults*: 3-8 mg/kg/day q 8 h to q 12 h (start at lowest dose).	*Adverse events*: Hypotension, dizziness, weakness, nausea, vomiting.
Digoxin (Lanoxin, cardioxin)	PO *Premature infant*: total digitalizing dose (TDD) 20 μg/kg, daily maintenance dose (DMD) 5 μg/kg *Term infant*: TDD, 30 μg/kg: DMD, 8-10 μg/kg < *2 yr*: TDD, 40-50 μg/kg; DMD, 10-12 μg/kg *2-10 yr*: TDD, 30-40 μg/kg; DMD 8-10 μg/kg > *10 yr*: TDD, 0.75-1.25 mg; DMD, 0.125-0.25 mg IM/IV dose: 75% of oral dose (except >10 yr); above doses are for congestive hearty failure; doses needed in supra-ventricular tachycardia may be higher therapeutic concentration: 0.8-2.0 ng/ml	*Elixir:* 0.05 mg/ml. *Injection:* 0.5 mg/2 ml. *Tablet:* 0.25 mg *Adverse events:* Nausea, vomiting, diarrhea, bradycardia, arrhythmias, yellow or green vision, vertigo, depression
Digoxin immune fab (Digibind)	*Infants, children, and adults*: dose is based on amount of digoxin of digitoxin ingested or estimated total body load (TBL) based on postdistributive serum concentration: TBL Digoxin = conc (ng/ml) × 5.6 × weight (kg)/1000. TBL digoxin = mg ingested × 0.8. TBL Digitoxin: conc (ng/ml) × 0.56 × wt (kg)/1000. TBL Digitoxin: mg ingested. Dose Digoxin Immune fab (mg) = TBL Digoxin × 76. Dose Digoxin: Immune fab (# vials) = TBL/0.5.	*Injection:* 40 mg/vial *Adverse events:* Worsening of heart failure or atrial fibrillation, hypokalemia, facial swelling.
Dihydrotachysterol, vitamin D_3	*Hypoparathyroidism* *Neonates*: 0.05-0.1 mg/day *Infants/young children*: 0.1-0.5 mg/day. *Older children/adults*: 0.5-1.0 mg/day; titrate dose to maintain serum calcium level at 8.5-10 mg/dl. *Renal hypophosphatemic rickets:* 0.25-1.0 mg/day. *Nutritional rickets:* 0.5 mg × 1 or 13-50 μg/day until healing occurs; ensure adequate intake of vitamin D thereafter. *Renal osteodystrophy:* 0.6-6 mg/day until healing occurs, then 0.125-0.6 mg/day.	*Adverse events:* Hypercalcemia, hypercalciuria, elevated serum creatinine.
Dimenhydrinate (Dramamine, draminate)	*Children* < *12*: 5 mg/kg/day q6h PO, IM *Adults:* 50-100 mg q4h to q6h PRN (maximum IM: 300 mg/day; maximum PO: *age 2-6 yr* —75 mg/day, age 6-12 yr—150 mg/day, > *12 yr to adult*: 400 mg/day).	*Injection:* 50 mg/ml. *Tablet:* 50 mg. *Syrup:* 15.625 mg/5 ml. *Adverse events:* Drowsiness, dizziness, hypotension, tachycardia.
Dimercaprol, British anti-Lewsite, BAL	*Arsenic or gold poisoning* *Mild:* days 1 and 2, 2.5 mg/kg q 6 h; day 3, 2.5 mg/kg q 12 h; day 4-14, 2.5 mg/kg qd *Severe:* days 1 and 2, 3 mg/kg q 4 h; day 3, 3 mg/kg q 6 h; day 4-14, 3 mg/kg q 12 h. *Lead poisoning* *Mild:* 3 mg/kg q 4 h × 5-7 days; use with edetate calcium disodium	*Injection:* 100 mg/2 ml. *Adverse events:* Nausea, vomiting, hypertension, tachycardia, blepharospasm, nephrotoxicity, headache, nervousness.

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Generic name (Trade name)	Dose/Route of administration	How supplied/major side effects
	Severe: 4 mg/kg q 4 h or 750 mg/m2/day q 4 h × 5-7 days use with edetate calcium disodium *Acute encephalopathy:* 4 mg/kg alone × 1, then q 4 h with 12.5 mg of edentate calcium disodium × 5-7 days. *Mercury poisoning:* 5 mg/kg × 1, followed by 2.5 mg/kg bid or qd × 10 days.	
Diphenhydramine (Benadryl)	*Children*: 5 mg/kg/day q 6 h PO or deep IM *Adults*: 10-50 mg q 6 h to q 8 h. *Anaphylaxis or Phenothiazine overdose* 1-2 mg/kg IV slowly (maximum: 300 mg/day).	*Capsules:* 25 mg. *Elixir:* 12.5 mg/5 ml. *Tablet:* 25 mg. *Adverse events:* Hypotension, tachycardia, dry mouth.
Diphenoxylate with Atropine (Lomotil, Lomofen)	*Children < 2 yr:* Do not use. *Children 2-12 yr:* 0.3-0.4 mg/kg/day bid or qid. *Adults:* 15-20 mg/day tid or qid; dose per diphenoxylate component.	*Tablet:* 2.5 + 0.025 mg *Adverse events:* Paralytic ileus, blurred vision, urinary retention, headache.
Dobutamine (Dobutrex, kardia)	*Continuous infusion:* 2.5-15 µg/kg/min (maximum 20 µg/kg/min) To prepare infusion: 6 × weight (kg) equals milligrams of drug to be added to 100 ml IV fluid; desired dose (µg/kg/min) equals IV infusion rate (ml/hr).	*Injection:* 250 mg/vial. *Adverse events:* Tachycardia, ectopic heart beats, tacchyarrhythmias, paraesthesias, leg cramps.
Domperidone (domstal, normodil, motinorm)	0.2-0.4 mg/kg/dose every 4-8 hr.	*Tablets:* 5, 10 mg. *Syrup:* 5 mg/ml. *Adverse events:* Gynecomastia, galactorrhea.
Dopamine	1-20 µg/kg/min IV infusion rate (ml/hr) = 6 × weight (kg) × desired dose (µg/kg/min)/mg drug per 100 ml IV fluid.	Injection: 40 mg/ml. *Adverse events:* Tachycardia, ectopic heart beats, vasoconstriction and gangrene, arrhythmias.
Doxapram (Dopram)	*Neonatal apnea* *Initial:* 1-1.5 mg/kg/hr *Maintenance:* 0.25-2.5 mg/kg/hr, titrate to lowest rate at which apnea is controlled. *Caution:* preparation contains benzyl alcohol 0.9% as a preservative	*Injection:* 20 mg/ml. *Adverse events*: Hypertension, tachycardia, arrhythmias, hyperpyrexia, hyperglycemia, seizures.
Doxycycline (Cedox, Doxy-1)	Children < 45 kg>7 yr: 4.4 mg/kg/day q 12 h × 1 day, then 2.2 mg/kg/day q 12 h to q 24 h Children > 45 kg and adults: 200 mg/day q 12 h × 1 day, than 100 mg/day q 12 h to q 24 hr (maximum: 300 mg/day).	*Tablets:* 100, 200 mg. *Syrups:* 25, 50 mg/5 ml. *Adverse events:* Teeth staining, diabetes insipidus, photosensitivity, nausea, vomiting, diarrhea.
Edrophonium (Tensilon)	*Diagnosis of myasthenia gravis* *Neonates:* 0.1 mg single dose *Infants and children:* Total dose of 0.2 mg/kg; 0.04 mg/kg initially as a test dose; if no reaction within 1 min, give remainder in 1 mg increments (maximum: 10 mg) *Adults:* 2 mg as test dose, then 8 mg after 45 sec if no reaction *Titration of therapy* *Children:* 0.04 mg/kg × 1 *Adults:* 2 mg × 1; if strength improves, an increase in the neostigmine or pyridostigmine dose is indicated *For SVT:* 0.1-0.2 mg/kg IV total dose; give 20% of dose every 2 min as needed.	*Injection:* 10 mg/ml. *Adverse events:* Arrhythmias, hypotension sweating, nausea, vomiting, laryngospasm, respiratory paralysis.

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Generic name (Trade name)	*Dose/Route of administration*	*How supplied/Minor side effects*
	Reversal of neuromuscular blockade (must be given with atropine) *Infants and children:* 1 mg/kg *Adults:* 10 mg over 30-45 sec; repeat as necessary (maximum: 40 mg)	
EDTA, calcium disodium versenate	Children Asymptomatic lead poisoning Initial course: 50 mg/kg/day q 6 h to q 12 h × 5 days; give with dimercaprol Subsequent course: 50 mg/kg/day q 8 h to q 12 h × 3-5 days; allow 2-3 wk between courses of therapy Symptomatic lead poisoning/lead encephalopathy Initial course: 75 mg/kg/day q 4 h × 5-7 days; give with dimercaprol; first dose should be preceded by initial dimercaprol dose by 4 hr. Subsequent course: as for asymptomatic poisoning above (maximum: 1 g/day) Note; Repeat course of therapy until blood level remains below 60 µg/dl. Adults: 2-4 g/day IV q 12 h to q 24 h × 5 days; may repeat course × 1 after interval of at least 2 days; more than 2 courses are not recommended.	*Injection:* 200 mg/ml. *Adverse events*: Arrhythmias, hypotension, seizures, headache, chills, hypokalemia, hypomagnesemia, hypocalcemia, nephrotoxicity, respiratory arrest.
Edetate Disodium	Hypercalcemic emergencies: 15-50 mg/kg/day (maximum: 3 g/day as indicated by serum calcium levels; allow 5 days between courses)	*Adverse events:* Arrhythmias, hypotension, seizures, nephrotoxicity, hypocalcemia, hypokalemia.
EMLA (Prilox cream)	For anesthesia of intact skin for needle procedure/ circumcision.	*Adverse effects:* In newborns it suppresses autonomic responses.
Enalapril (Envas, minipril)	*Infants:* 0.1 mg/kg/day, increasing to 0.12-0.43 mg/kg/day. *Adults:* 5 mg PO qd initially (maximum: 40 mg/day)	*Tablets:* 2.5, 5, 10, 20 mg. *Adverse events:* Hypotension, tachycardia, cough, hyperkalemia, syncope.
Epinephrine hydrochloride (Adrenaline)	*Neonates:* IV, intratracheal: 0.01-0.03 mg/kg (0.1-0.3 ml/kg of 1: 10, 000 solution) every 3-5 min. *Infants and children:* SC: 0.01 mg/kg (0.01ml/kg/dose of 1: 1000 solution) IV: 0.01 mg/kg (0.1 ml/kg of 1: 10, 000 solution (max 1 mg). Intratracheal: 0.1 mg/kg/dose (0.1 ml/kg of 1: 1000 solution) (max 0.2 ml/kg). *Continuous infusion:* 0.1-1 µg/kg/min per response. *Nebulization:* 0.25-0.5 ml of 2.25% racemic epinephrine diluted in 3 ml normal saline. *Ophthalmic:* Instil 1-2 drops in eye(s) 1-2 times daily. *Adults:* IV: 1-5 mg 3-5 min. *Intratracheal:* 1 mg initial, max 12.5 mg/dose. IM, SC: 0.1-0.5 mg every 10-15 min. *Continuous infusion:* 1-10 µg/min. *Ophthalmic:* instil 1-2 drops in eye(s) 1-2 times daily.	*Injection:* I mg/ml 1: 1000 dilution *Aerosol:* *Adverse events*: Tachycardia, hypertension, nervousness, restlessness, irritability, headache, tremor, weakness, nausea, vomiting, acute urinary retention.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Ergocalciferol, calciferol, vitamin D_2	*Premature infants:* 10-20 µg/day. *Renal failure:* *Children:* 100-1000 µg/day. *Adults:* 500 µg/day. *Hypoparathyroidism:* *Children:* 1.25-5 mg/day. *Adults:* 0.625-5 mg/day. *Rickets:* *Children:* 75-125 µg/day. *Adults:* 0.25-1.5 mg/day.	*Adverse events:* Hypercalcemia, weakness, lethargy, hypertension, arrhythmias, mild acidosis, hypercholesterolemia, nausea, vomiting, constipation, nephroclcinosis, photophobia
Erythromycin (Althrocin, E-mycin)	*Neonates:* postnatal age ≤ 7 days: 20 mg/kg/day PO divided q 12 h; > 7 days < 1200 g: 20 mg/kg/day divided q 12 h; ≥ 1200 g: 30 mg/kg/day PO divided q 8 h. *Children:* max dose 2 g/day: *Base:* 30-50 mg/kg/day PO divide q 6-8 h. *Estolate:* 30-50 mg/kg/day PO divided q 8-12 h. *Stearate:* 20-40 mg/kg/day PO divided q 6 h. *Lactobionate:* 20-40 mg/kg/day IV divided q 6-8 h. *Gluceptate:* 20-50 mg/kg/day divided q 6 h: max dose IV 4 g/day. *Adults:* Base 333 mg PO q 8 h, estolate/stereate/base 250-500 mg PO q 6 h.	*Tablets:* 100, 125, 250, 500 mg. *Suspension:* 100, 125 mg/5 ml. *Adverse events:* abdominal cramping, nausea, vomiting, diarrhea, cardiac toxicity (IV use)
Esmolol (Miniblock)	*Children:* 100-500 µg/kg over 1 min then continuous infusion 200-1000 µg/kg/min. *Adults:* 500 µg/kg over 1 min then continuous infusion 50-200 µg/kg/min.	*Injection:* 100 mg/ml. *Contraindication:* Sinus bradycardia, heart block, uncompensated heart failure. *Adverse events:* Hypotension, bradycardia, Raynaud phenomenon, dizziness, confusion, lethargy, bronchoconstriction.
Ethacrynic Acid (Edecrin, ethacrin)	*Children:* Oral 1-3 mg/kg/day. IV: 0.5-1 mg/kg/dose every 8-24 hr. *Adults:* Oral 25-400 mg/day. IV: 0.5-1 mg/kg/dose every 8-24 hr.	*Tablet:* 50 mg. *Injection:* 50 mg/vial. *Adverse events:* Hypotension, fluid and electrolyte depletion, hyperuricemia, ototoxicity, tinnitus.
Ethambutol (Albutol, mycobutol)	*Children:* 15 mg/kg/day PO qd. *Adult:* 15 mg/kg/day PO qd; max dose 2.5 g/day.	*Tablet:* 200, 400, 600, 800 mg. *Adverse events:* Optic neuritis, decreased visual acquity, headache, dizziness, rash, peripheral neuropathy.
Ethionamide (Myobid)	*Children:* 15-20 mg/kg/day PO divide q 8-12 h (max dose 1000 mg/day) *Adult:* 500-1000 mg PO q 8-12 h.	*Tablet:* 250 mg. *Adverse events:* GI upset, hepatotoxicity, vit B6 deficiency, dizziness, headache, metallic taste, optic neuritis.
Ethosuximide (Zarontin)	*Children:* < 6 yr: start 15 mg/kg/day in 2 doses; increase every 4-7 days to therapeutic level, usually 15-40 mg/kg/day in 2 doses. Max 1.5 g/day. > 6 yr and adults: start 250 mg twice daily; increase by 250 mg/day every 4-7 days up to therapeutic level or 1.5 g/day.	*Syrup:* 250 mg/ml. *Tablet:* 250 mg. *Adverse events:* Sedation, lethargy, nausea, vomiting, anorexia, abdominal pain, leucopenia, thrombocytopenia, aplastic anemia. *Therapeutic level:* 40-100 µg/ml; toxic 150 µg/ml.
Factor VIIa (Novoseven)	1.2 mg, 2.4 mg, 4.8 mg vials 0.6 mg/ml (600 µg/ml) *Single dose:* 352 to 800 µg/kg IV	Hypersensitivity thrombosis stroke.
Famotidine (Facid, famocid)	*Infants and children:* Oral, IV 1-2 mg/kg/day in 1-2 doses; max 40 mg/day.	*Adverse events:* GI discomfort, thrombo cytopenia, increased liver enzymes.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	Adults: Oral 40 mg/day at bedtime, IV 20 mg every 12 hr. *Tablets:* 20, 40 mg. *Suspension:* 40 mg/5 ml.	
Fentanyl citrate (Fendrop)	*Neonates and infants:* IV 1-4 µg/kg/dose, may repeat every 2-4 hr or continuous infusion 0.5-5 µg/kg/hr. Children 1-12 yr: Pain: IM, IV 1-3 µg/kg/dose, may repeat every 30-60 min; continuous infusion 1-5 µg/kg/hr. Children > 12 yr and adults: pain: IV, IM 0.5-1 µg/kg/dose, may repeat in 30-60 min. Transdermal 25-100 µg/hr system as needed for relief. Oral 5 µg/kg or 400 µg (whichever is less) Anesthesia: IV, IM 2-50 µg/kg.	*Injection:* 50 µg/ml. *Oralet lozenge:* 200, 300, 400 µg. *Adverse events:* Hypotension, bradycardia, CNS depression, constipation, biliary tract spasm, nausea, vomiting, urinary tract spasm, respiratory depression.
Fluconazole (Syscan, Zocon)	*Neonate:* thrush 6 mg/kg, IV, PO qd first day then 3 mg/kg/day qd for 14-21 days. *Systemic infections:* postnatal age < 14 days 6-12 mg/kg/day PO, IV q 72 h; > 14 days once daily. *Children:* 6-12 mg/kg/day IV, PO qd; *Cryptococcal meningitis* 12 mg/kg/day first day then 6-12 mg/kg/day IV, PO q day.	*Tablets:* 50, 100, 150, 200 mg. *Injection:* 2 mg/ml. *Adverse events:* Dizziness, rash, nausea, abdominal pain, elevated liver enzymes
Flucytosine (Ancobon)	*Neonate:* 50-100 mg/kg/day PO divided q 12-24 h. *Children and adults:* 100-150 mg/kg/day PO divided q 6-8 h. Monitor blood levels.	*Tablet:* 500 mg. *Injection:* 10 mg/ml. *Adverse events:* Confusion, rash, nausea, vomiting, bone marrow suppression, elevated liver enzymes.
Fludrocortisone (Florinef)	*Infants and children:* 0.05-0.1 mg/day. *Adults:* 0.05-0.2 mg/day.	*Tablet:* 100 µg. *Adverse events*: Hypertension, edema, heart failure, convulsions, hypokalemia, peptic ulcer, muscle weakness, HPA-axis suppression.
Flumazenil (Mazecan)	*Children:* 0.005-0.01 mg/kg load, then as continuous infusion 0.005-0.001 mg/kg/hr (max cumulative dose 1 mg)	*Adverse events:* arrhythmias, hypo or hypertension, seizures.
Folic Acid (Folvite, folacin)	*Neonates:* To 6 mo: oral 25-35 µg/day. 6 mo-3 yr: 50 µg/day. 4-6 yr: 75 µg/day. 7-10 yr: 100 µg/day. 11-14 yr: 150 µg/day. > 15 yr and adults: 200 µg/day. *Folate deficiency:* 1 mg/day.	*Tablet:* 5 mg.
Furosemide (lasix, salinex)	*Premature infants:* 0.5-2 mg/kg IV or 1-4 mg/kg oral every 12-48 hr (dose to response). *Infants and children:* 1-2 mg/kg IV or 1-4 mg/kg oral every 6 to 24 hr or continuous infusion 0.05 mg/kg/hr (dose to response). *Adults:* 10-600 mg/day in 1-4 divided doses; or continuous infusion 0.05 mg/kg/hr (dose to response).	*Tablets:* 40, 500 mg. *Injection:* 20 mg/2 ml. *Adverse events*: Dehydration, electrolyte loss, hyperuricemia, ischemic hepatitis, hypercalciuria, renal stones, ototoxicity, photosensitivity.
Gabapentin (Gabantin, neurontin)	*Initial dose:* 15 mg/kg/day q 8 h. Increase over several days to 30-60 mg/kg/day q 8 h.	*Capsules:* 300, 400 mg. *Adverse effects:* Somnolence, ataxia, fatigue, nausea, dizziness, diplopia, nystagmus.
Ganciclovir (Cytovene)	CMV retinitis: *Children and adults:*	*Injection:* 500 mg/vial. *Adverse events:* Headache, seizures,

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Generic name (Trade name)	*Dose/Route of administration*	*How supplied/Major side effects*
	Induction therapy: 10 mg/kg/day IV (over 1-2 hr) divided q 12 h for 14-21 days; maintenance therapy: 5-6 mg/kg/day IV once daily. CMV disease and prophylaxis (solid organ transplant) *Induction:* 10 mg/kg/day divided q 12 h for 7-14 days then 5-6 mg/kg/day IV once daily.	hypertension, nausea, marrow suppression, renal/liver toxicity, rash, photophobia.
Gentamicin (Genticyn, garamycin)	*Neonates:* IM, IV (over 30-60 min): Postnatal age ≤ 7 days 1200-2000 g: 2.5 mg/kg q 12-18 h; > 2000 g: 2.5 mg/kg q 12 h; postnatal age > 7 days 1200-2000 g 2.5 mg/kg q 8-12 h; > 2000 g: 2.5 mg/kg q 8 h. *Children:* 2.5 mg/kg/day divided q 8-12 h. Alternatively may administer 5-7.5 mg/kg/day IV once daily. Intrathecal preservative-free preparation for intraventricular or intrathecal use: neonate 1 mg/day; child 1-2 mg/day; adult 4-8 mg/day. *Adults:* 3-6 mg/kg/day divided q 8 h.	*Injection:* 10, 40 mg/ml. *Adverse events:* Ototoxicity, nephrotoxicity.
Glucagon	*Neonates:* 0.3 mg/kg/dose (max 1 mg) IV, IM, SC. *Children:* 0.025-0.1 mg/kg/dose (max 1 mg), may repeat in 20 min. *Adults:* 0.5-1 mg, may repeat in 20 min as needed.	*Injection:* 1, 10 mg/vial. *Adverse events:* Nausea, vomiting, hypersensitivity reactions.
Glycopyrrolate (Pyrolate)	*Children:* *Control of secretions:* Oral 40-100 µg/kg/dose 3-4 times/day. IM, IV 4-10 µg/kg/dose every 3-4 hrs. *Preoperative IM:* 4.4-8.8 µg/kg/dose 30-60 min before procedure.	*Injection:* 0.2 mg/ml. *Adverse events:* Tachycardia, nervousness, headache, insomnia, drowsiness, dry mouth, constipation, urinary retention, blurred vision.
Haloperidol (Depidol, serenace)	*Children 3-12 yr:* Oral: start 0.25-0.5 mg/day in 2-3 divided doses, then increase weekly by 0.25-0.5 mg daily based on response to max 0.15 mg/kg/day. 6-12 yr: IM: 1-3 mg/dose every 4-8 hr (max 0.15 mg/kg/day). *Adults:* Oral: 0.5-5 mg 2-3 times daily. IM: 2-5 mg every 4-8 hr.	*Tablets:* 0.25, 1.5, 5, 10, 20 mg *Injection:* 5 mg/ml. *Adverse events:* Drowsiness, restlessness anxiety, extrapyramidal symptoms, dystonia, akathesia, tardive dyskinesia, hypotension, arrhythmias, seizures, cholestatic liver disease, agranulocytosis, leukopenia.
Heparin (unfractionated)	*Neonates, infants and children:* *Thrombosis and ECMO:* Load 50 units/kg IV bolus and 15-35 units/kg/hr continuous infusion maintenance dose (adjust to target APTT and heparin level). Catheter patency: 0.5-1 unit/ml. *Adults:* load 70-100 units/kg/hr IV push, continuous infusion; SC 5000 units every 8-12 hr for prophylaxis.	*Injection:* 1000, 5000 units/ml, 0.83 = 100 units *Adverse events:* Bleeding, thrombocytopenia, thrombosis.
Hepatitis B immunoglobulin (Hepaglob)	Percutaneous inoculation: 0.06 ml/kg IM (maximum: 5 ml) × 1 within 24 hr of exposure; give with Hepatitis B vaccine.	*Injection:* 100 IU/0.5 ml, 200 IU/1 ml. *Adverse effects:* Itching, mild pain at injection site.
Hyluronidase (Hynidase)	*Neonates, infants and children:* inject using 25-26 gauge needle (total 1 ml, 150 U) SC or intradermal at 5 sites (0.2 ml to each) at leading edge of extravasation.	*Injection:* 1500 IU/ampoule. *Adverse events:* Tachycardia, hypotension erythema.
Hydralazine (Nepresol, zinepress, apresoline)	*Neonates:* IV 0.1-0.5 mg/kg/dose every 6-8 hr. *Oral:* 0.25-1 mg/kg/dose every 6-8 hr. *Infants and children:* IM, IV start 0.1-0.2 mg/kg/dose every 4-6 hr and titrate to effect (max 3.5 mg/kg/day). Oral 0.75-1 mg/kg/day in 2-4 divided doses (max 7.5 mg/kg/day).	*Tablets:* 25, 50 mg *Injection:* 20 mg/ml. *Adverse events:* Palpitations, flushing, tachycardia, nausea, vomiting, anorexia, diarrhea, lupus like syndrome, arthralgias, peripheral neuropathy.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	Adults: IM, IV 10-20 mg/dose every 4-6 hr (max 40 mg/dose). Oral 10-25 mg/dose 4 times daily and titrate to effect.	
Hydrochlororthiazide (Esidrex, hygrotone)	*Neonates and infants:* 2-4 mg/kg/day in 2 divided doses. Infants > 6 mo and children: 2 mg/kg/day in 2 divided doses. Adults: 12.5-100 mg/day.	*Tablets:* 25, 50, 100 mg. *Adverse events:* Hypokalemia, hypochloremia, hypomagnesemia, hyperuricemia, hyperlipidemia, pancreatitis, thrombocytopenia, aplastic anemia, intrahepatic cholestasis.
Hydrocortisone (Efcorlin, lycortin)	*Neonates, infants, young children:* *Adrenal insufficiency:* 1-2 mg/kg IV bolus, then 25-150 mg/day divided every 6 hr. *Congenital adrenal hyperplasia:* IV 0.5-0.7 mg/kg/day start, then 0.3-0.4 mg/kg/day maintenance therapy, give doses as ¼ in AM, ¼ at noon and ½ at night. *Shock:* IV 35-50 mg/kg, then 50-150 mg/kg/day divided every 6 hr for 48-72 hr. *Infants and older children:* *Adrenal insufficiency:* 1-2 mg/kg IV bolus, then 150-250 mg/day divided every 6-8 hr. *Anti-inflammatory:* IV, IM 1-5 mg/kg/day in 1-2 doses; oral 2.5-10 mg/kg/day divided every 6-8 hr. *Shock:* IV 50 mg/kg/dose every 4 hr. *Status asthmaticus:* IV 1-2 mg/kg/dose every 6 hr. *Adults:* *Anti-inflammatory:* IV, IM, Oral 15-240 mg/dose every 12 hr. *Shock:* IV 0.5-2 g every 2-6 hr. *Rectal:* 1 application 1-2 times/day for 2-3 wk. *Topical:* apply 3-4 times/day.	*Tablets:* 10, 20 mg. *Injection:* 100 mg/vial. *Adverse events:* Hypertension, hyperglycemia, hypokalemia, euphoria, insomnia, cushing syndrome, peptic ulcer, cataracts, immunosuppression, acne, skin and muscle atrophy, edema.
Ibuprofen (Ibugesic, brufen, febrilix)	*Children* *Pain, fever:* 5-10 mg/kg/dose every 6-8 hr. Juvenile rheumatoid arthritis: 30-50 mg/kg/day in 4 divided doses. *Adults:* 400-800 mg/dose 3-4 times daily (max 3.2 g/day)	*Tablets:* 200, 400, 600 mg. *Syrup:* 100 mg/5 ml. *Adverse events:* Heart burn, nausea, GI bleeding, GI perforation, edema, hypertension, tachycardia, acute renal failure.
Imipenem-cilastin (Primaxin)	*Neonate:* Postnatal age ≤ 7 days < 1200 g 20 mg/kg IM, IV q 18-24 h; 1200 g 40 mg/kg divided q 12 h; postnatal age > 7 days 1200-2000 g 40 mg/kg q 12 h; 2000 g 60 mg/kg q 8 h. *Children:* 60-100 mg/kg/day divided q 6-8 h. *Adults:* 2-4 g/day divided q 6-8 h (max dose 4g/day).	*Injection:* 500, 1000, 1500 mg containing 250, 500, 750 mg of imipenem respectively. *Adverse events:* Nausea, seizures, rash.
Imipramine (Depsonil, antidep)	*Children:* Tablet: 25 mg. *Depression:* start 1.5 mg/kg/day, may increase by 1 mg/kg/day every 3-4 days (max 5 mg/kg/day) *Enuresis:* >6 yr, 10-25 mg at bedtime. *Cancer pain:* 0.2-0.4 mg/kg at bedtime, may increase dose 50% every 3-4 days (max 3 mg/kg). *Adolescents:* Oral: start 25-50 mg/day, may gradually increase to max 200 mg/day.	*Capsules:* 25, 75 mg. *Adverse events:* Arrhythmias, sedation, postural hypotension, constipation, dry mouth, seizures, urinary retention, increased liver enzymes.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	Adults: Oral 25 mg 3-4 times daily, may increase dose gradually to max 300 mg/day; IM initial up to 100 mg in divided doses.	
Immune globulin (Sandoglobulin, ZY-IVGG)	*Neonates:* 500-750 mg/once. *Children and adults:* *Immunodeficiency syndrome:* 100-400 mg/kg/dose every 2-4 wks. *Chronic lymphocytic leukaemia:* 400 mg/kg/dose every 3 wks. *Idiopathic thrombocytopenic purpura:* 1000 mg/kg/dose for 2-5 consecutive days then every 3-6 wk. *Kawasaki disease:* 2 g/kg single dose. *CMV infection:* 500 mg/kg/dose every other day for 7 doses. *Severe systemic infection:* 500-1000 mg/kg once a wk. *Polyneuropathy:* 1 g/kg/day for 2 consecutive days each month.	*Injection:* 1, 2.5, 3, 6 gm *Adverse events:* Flushing, tachycardia, chills, nausea, fever, hypersensitivity reactions, headache, aseptic meningitis, dyspnea.
Indomethacin (Idicin, indocap, indocin)	*Neonates:* IV 0.1-0.25 mg/kg/dose every 12 hr for 3-6 doses. *Inflammatory rheumatoid disorders:* *Children:* 1-2 mg/kg/day in 2-4 doses (max 4 mg/kg/day). *Adults:* 25-50 mg/dose 2-3 times/day (max 200 mg/day).	*Capsule:* 25 mg *Capsule SR:* 75 mg. *Injection:* 1 mg/vial. *Adverse events:* Confusion, dizziness, headache, vomiting, abdominal pain, GI ulceration, bone marrow suppression, impaired platelet aggregation, renal failure, hyperkalemia, hypertension.
Insulin	*Neonates*: Regular insulin 0.01-0.1 units/kg/hr continuous infusion, or SC 0.1-0.2 units/kg every 6-12 hr. *Children and adults*: 0.5-1 unit/kg/day. Adjust doses to blood glucose and hemoglobin AIC results. *Adolescents*: 0.8-1.2 units/kg/day. Diabetic ketoacidosis: Continuous infusion IV 0.1 units/kg/hr adjusted to serum glucose. *Hyperkalemia:* Try calcium gluconate and $NaHCO_3$ first, then dextrose 50% 0.5-1 ml/kg and regular insulin 1 unit per 4-5 g dextrose.	*Soluble insulins:* 40, 80 IU/ml, 10 ml/vials *Zinc suspension insulin:* 40, 80 IU/ml, 10 ml vials. *Isophane insulin:* 40, 80 IU/ml, 10 ml vials. *Protamine zinc insulins:* 40 IU/ml, 10 ml vial. *Adverse events:* Hypoglycemia and associated symptoms, hypokalemia.
Ipecac	*Children:* May repeat dose in 20 min one time. 6-12 mo: 5-10 ml followed by 20 ml/kg of water. 1-12 yr: 15 ml followed by 20 ml/kg of water. > 12 yr and adults: 30 ml followed by 300 ml of water.	*Adverse events:* Lethargy, persistent vomiting, diarrhea.
Ipratropium (Ipravent)	*Neonates:* Nebulized 100 µg/dose or MDI 1-2 puffs 3-4 times/day. *Infants and children:* Nebulized 125-250 µg/dose or MDI 1-2 puffs 3-6 times/day. *Adults*: Nebulized 500 µg/dose or MDI 2 puffs 3-4 times daily. *Nasal spray for rhinitis:* 1-2 sprays in each nostril 2-3 times daily.	*Respirator solution:* 250 µg/ml. *Inhaler:* 20 µg/metered dose. *Adverse events:* Dry mouth, nervousness, dizziness, blurred vision, urinary retention.
Isoniazid, INH (Isonex, isokin)	*Children:* 10-20 mg/kg/day PO divided q12-24 hr; max dose 300 mg/day; prophylaxis dose 10 mg/kg/day. *Adult:* 5 mg/kg/day PO once daily; usual max dose 300 mg/day.	*Tablets:* 100, 300 mg. *Syrup:* 100 mg/5 ml. *Adverse events:* Dizziness, seizure, rash, hepatotoxicity, peripheral neuropathy, GI upset.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Isoproterenol (Isoprin)	*Neonates, infants and children*: IV infusion 0.05-2 µg/kg/min. *Children*: MDI 1-2 puffs every 4 hr as needed; nebulize 0.01 ml of 1% solution; SL tablets 5-10 mg every 3-4 hr (max 30 mg/day). *Adults:* MDI 1-2 puffs 4-6 times/day; nebulize 0.25-0.5 ml of 1% solution; SL tablets 10-20 mg every 3-4 hr (max 60 mg/day); IV infusion 2-20 µg/min.	*Injection:* 4 mg/2 ml, 0.2 ml/ml. *Adverse events:* Tachycardia, palpitations, restlessness, anxiety, headache, insomnia, *Adverse effects:* GI distress, nausea, paradoxical bronchospasm
Ketamine (ketamax, ketamin)	Oral 6-10 mg/kg; IM 3-7 mg/kg; IV 0.5-2 mg/kg. *Adults:* 3-8 mg/kg; IV 1-4.5 mg/kg (supplemental doses are 1/3 of initial dose).	*Injection:* 10, 50 mg/ml in 2, 10, 20 ml vials *Adverse events:* Hypertension, tachycardia, hypotension, bradycardia, delirium, hallucinations, respiratory depression, emergence reactions.
Ketorolac (Ketoral, ketanov)	*Children 2-16 yr:* IM, IV 0.4-1 mg/kg/dose. Oral 1 mg/kg/dose every 6 hr if needed. *Adults:* IM 60 mg, IV 30 mg up to every 6 hr as needed. *Ophthalmic:* 1 drop in eye 4 times/day for up to 7 days.	*Tablet:* 10 mg. *Injection:* 30 mg/ml. *Adverse events:* Edema, somnolence, dizziness, headache, GI pain, acute renal failure, impaired platelet aggregation.
Ketoconazole (funazole, nizoral)	*Children > 2 yr:* 3.3 mg/kg/day *Adults:* 200-400 mg/day qd (max 1g/day) *Topical:* Apply sufficient quantity to cover affected area qd × 2 wk.	*Tablet:* 200 mg. *Suspension:* 100 mg/5 ml. *Adverse effect:* Hepatotoxicity.
Labetalol (Normadate, trandate)	*Children:* Oral start 4 mg/kg/day in 2 doses, then gradually increase (max 40 mg/kg/day). IV start 0.2-1 mg/kg/dose (max 20 mg/dose). *Adults:* Oral 100 mg twice daily, may increase every 2-3 days (max 2.4 g/day). IV start 20 mg, repeat boluses 40 mg every 10 min (max total dose 300 mg), continuous infusion 2 mg/min and titrate to response.	*Tablet:* 50, 100, 200, 400 mg. *Injection:* 5 mg/ml. *Adverse events:* Orthostatic hypotension, CHF, conduction disturbance, bradycardia, fatigue, dry mouth, nasal congestion, bronchospasm.
Lactulose (Livoluk, duphalac)	*Infants:* 2.5-10 ml/day in 3-4 doses. *Children:* 40-90 ml/day in 3-4 doses. *Adults:* 30-45 ml/dose 3-4 times/day.	*Syrup:* 10 g/15 ml. *Adverse events:* Flatulence, dirrhoea, nausea, vomiting.
Lamotrigine (Lametec, lamitor)	*Children 2-16 yr:* 2 mg/kg/day in 2 doses for 2 wk, then 5 mg/kg/day in 2 doses for 2 wk, then 10 mg/kg/day in 2 doses if needed (usual 5-15 mg/kg/day, max 400 mg/day). *If patient is on valproate:* 0.2 mg/kg/day in 2 doses for 2 wk, then 0.5 mg/kg/day in 2 doses for 2 wk, then 1 mg/kg/day in 2 doses (max dose 5 mg/kg/day). *Adults:* start 50 mg/day for 2 wk, then 100 mg/day, then increase by 100 mg/day at weekly intervals to response (max 500 mg/day). *If patient is on valproate:* 25 mg every other day for 2 wk, then increase by 25 mg/day every week to response (max 150 mg/day)	*Tablets:* 5, 25 mg. *Adverse events:* Rash, dizziness, sedation, exacerbation of seizures, angioedema, photosensitivity, nystagmus, amblyopia, nausea, vomiting.
Levo-Carnitine (Carnitor)	*Adults:* Oral 990 mg q 8-12 hr. *Infants and children:* 50-100 mg/kg/day = 0.5 ml/kg/day in divided doses.	*Syrup:* 500 mg/5 ml. *Tablet:* 330 mg. *Adverse effects:* Nausea, vomiting, abdominal cramps, diarrhea.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Levothyroxine (Eltroxin, thyrox)	*Oral:* 0-6 mo: 8-10 µg/kg/day. 6-12 mo: 6-8 µg/kg/day. 1-5 yr: 5-6 µg/kg/day. 6-12 yr: 4-5 µg/kg/day. > 12 yr: 2-3 µg/kg/day. *Adults:* 12.2-50 µg/day (max 200 µg/day). IV, IM 50-75% of oral dose. *Myxedema coma:* 200-500 µg for 1 dose. *Thyroid suppression therapy:* 2-6 µg/kg/day for 7-10 days.	*Tablets:* 25, 50, 100, 200 µg. *Adverse events:* Tachycardia, arrhythmias, hypertension, insomnia, hair loss, increased appetite, weight loss, tremor, sweating.
Lidocaine (Xylocard, gesicard)	*Children and adults: Topical:* Apply to affected area (max 3 mg/kg/dose) at least 2 hr apart. Local anesthetic injection: doses per need, max 4.5 mg/kg not closer than 2 hr apart. *Arrhythmias:* *Children:* load 1 mg/kg (may repeat every 5-10 min to max 3 mg/kg), IV continuous infusion. 20-50 µg/kg/min (½ dose if liver disease or poor cardiac output). *Adults:* 1-1.5 mg/kg load (may repeat to max 3 mg/kg), IV continuous infusion 2-4 mg/min. *ET route:* 2-2.5 times IV dose. Prehospital post-MI: 300 mg IM.	*Injection:* 2% 50 ml vial, 1 ml = 21.33 mg). *Adverse events:* Arrhythmias, heart block, lethargy, coma, seizures, nausea, vomiting, paraesthesias, blurred vision, rash.
Linezolid (Zyvox, linospan)	200 mg/100 ml, 600 mg tablets 10 mg/kg q 12° oral or intravenous *Duration* — for VRE: 14-28 days MRSA 10-14 days VRE: Vancomycin resistant enterococcus MRSA: Methicillin resistant S. Aureus	Rash, vomiting thrombocytopenia anemia, leukopenia and pancytopenia
Loperamide (Imodium, imosec)	2-5 yr: 1 mg 3 times/day. 6-8 yr: 2 mg 2 times/day. 8-12 yr: 2 mg 3 times/day. *Adult:* 4 mg initially, then 2 mg after each loose stool (max 16 mg/day).	*Tablet:* 2 mg. *Liquid:* 1 mg/5 ml. *Adverse events:* Sedation, fatigue, dizziness, nausea, vomiting, constipation.
Lorazepam (Ativan, larpose)	*Antiemetic therapy* *Children:* IV 0.04-0.08 mg/kg/dose every 6 hr as needed *Anxiety/sedation* *Neonates:* IV 0.1-0.4 mg/kg/dose every 4-6 hr as needed *Infants and children:* IV 0.05-0.1 mg/kg/dose every 4-8 hr. *Adults:* Oral 1-10 mg/day in 2-3 divided doses. *Insomnia* *Adults:* 2-4 mg at bedtime. *Status epilepticus* *Neonates:* IV 0.05-0.2 mg/kg/dose over 2-5 min, may repeat in 10-15 min. *Infants and children:* IV 0.1 mg/kg load over 2-5 min, may give additional 0.05 mg/kg bolus in 10-15 min. *Adolescent:* IV 0.07 mg/kg/dose over 2-5 min, may repeat in 10-15 min. *Adults:* IV 4 mg/dose over 2-5 min, may repeat in 10 min.	*Tablet:* 1, 2 mg. *Injection:* 2 mg/ml. *Adverse events:* Myoclonus, tachycardia, drowsiness, paradoxical excitement, blurred vision, diplopia.
L- Ornithine-L-Aspartate (Hepamerz)	*Children:* 1-3 satchets q 12 hr.	*Adverse effects:* nausea, vomiting.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Magnesium sulphate	*Hypomagnesemia* *Neonates*: IV 25-50 mg/kg/dose every 8 hr for 2-3 doses *Children*: Oral 100-200 mg/kg/dose 4 times daily; IM, IV 25-50 mg/kg/dose every 6 hr for 3-4 doses. *Adults*: Oral 3 g every 6 hr for 4 doses; IM, IV 1 g every 6 hr for 4 doses. *Daily maintenance magnesium:* *Neonates, infants and children*: IV 30-60 mg/kg/day. *Adolescents*: IV 42-54 mg/kg/day. *Adults*: IV 0.5-3 g/day. Infuse IV doses over 2-4 hr (max 125 mg/kg/hr). *Management of seizures and hypertension* *Children*: IM, IV 20-100 mg/kg/dose every 4-6 hr as needed. *Cathartic* *Children*: Oral 0.25 g/kg/dose. *Adults*: Oral 10-30 g.	*Injections:* 1%, 10%, 25%, 50% 1 ml ampoules. *Adverse events:* Hypotension, abdominal-cramps, muscle weakness, CNS depression, heart block, respiratory paralysis.
Mannitol	*Children and adults:* IV 200 mg/kg test dose, initial 0.5-1 g/kg, maintenance 0.25-0.5 g/kg every 4-6 hr.	*Injection:* 20%. *Adverse events:* Circulatory overload, headache, seizures, fluid and electrolyte imbalance
Menadione sodium diphosphate, vitamin K4 (Kapilin)	*Hemorrhagic disease of newborn (prophylaxis):* 1 mg IM × 1 immediately after birth. *Hypoprothrombinemia* *Infants:* 2.5-5 mg; repeat q12-24h IM, IV. *Children:* 5-10 mg; repeat q12-24h IM, IV. *Adults:* 5-15 mg qd or bid. *Maintenance in patients with persistent cholestasis:* 2.5-5 mg qd.	*Injection:* 10 mg/ml.
Mepridine (Pethidine hydrochloride)	*Children:* IM, IV, SC 1-1.5 mg/kg/dose every 3-4 hr. *Adults:* IM, IV, SC 50-100 mg/dose every 3-4 hr as needed (equipotent oral dose is 3 times IV dose).	*Injection:* 50 mg/ml. *Adverse events:* Hypotension, weakness headache, anorexia, hallucination, seizures, dependence.
Meropenem (Meronem, merotrol, merrem)	60-120 mg/kg/day divided q 8°	Vomiting, pain at injection site Neutropenia incidence of seizures less than imepenem
Methadone	*Neonates (abstinence syndrome)* 0.05-0.2 mg/kg/dose every 12 hr then adjust/taper based on abstinence scores. *Children:* analgesia: IV, IM, oral 0.1 mg/kg/dose every 4 hr for 2-3 doses, then every 6-12 hr as needed. *Narcotic abstinence:* start 0.05-0.1 mg/kg/dose every 6 hr and taper as per abstinence scores. *Adults:* IV, IM, SC, oral *Analgesia:* 2.5-20 mg every 6-8 hr. *Detoxification:* 15-40 mg/day.	*Adverse events:* Weakness, drowsiness, dizziness, nausea, vomiting, constipation, ileus.
Methimazole	*Children* start: 0.4 mg/kg/day, then maintenance 0.2 mg/kg/day. *Adults* start: 5 mg/kg every 8 hr, maintenance dose 5-15 mg/day (max 60 mg/day).	*Adverse events:* Fever, skin rash, leukc penia, agranulocytosis, SLE-like syndrome nausea, vomiting, cholesta jaundice, constipation, weight gain.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Methohexital	*Children:* IM (preoperative) 5-10 mg/kg/dose; IV (induction) 1-2 mg/kg/dose. Rectal 20-35 mg/kg/dose. *Adults:* IV (induction) 50-120 mg, then 20-40 mg every 4-7 min.	*Adverse events:* Respiratory depression, laryngospasm, hypotension, skeletal rigidity, seizures, tremor, vomiting.
Methylene blue	*Children and adults:* *Methemoglobinemia:* IV 1-2 mg/kg, may repeat after 1 hr if needed. NADPH-methemoglobin reductase deficiency: Oral 1-1.5 mg/kg/day (given with 5-8 mg/kg/day of ascorbic acid).	*Adverse events:* Urine and faeces turn blue green, anaemia.
Methylphenidate (Ritalin)	*Children:* > 5 yr: 0.3-0.6 mg/kg/dose (max 2 mg/kg/day). *Adults:* 10 mg 2-3 times/day (max 60 mg/day).	*Tablet:* 5, 10, 20 mg. *Adverse events:* Insomnia, agitation, weight loss, tachycardia, hypertension, addiction, tics.
Methylprednisolone (Medrol, unidrol)	*Children*: *Anti-inflammatory and immunosuppressant:* Oral, IM, IV 0.5-2 mg/kg/day divided every 6-12 hr. *Lupus nephritis:* IV 30 mg/kg every other day for 6 doses. *Acute spinal cord injury*: 30 mg/kg over 15 min, followed in 45 min by continuous infusion of 5.4 mg/kg/hr for 23 hr. *Adults*: Oral 2-60 mg/day in 1-4 doses. IV 40-250 mg every 4-6 hr. IM 10-80 mg once daily.	*Tablet:* 2, 4, 16 mg. *Injection:* 140, 500, 1000, 2000 mg. *Adverse events:* Hypertension, edema, psychosis, pseudotumor cerebri, hyperglycemia, hypokalemia, alkalosis, cushing syndrome, skin atrophy, peptic ulcer, cataracts, glaucoma.
Metoclopramide (Perinorm, reglan)	*Neonates, infants and children:* GER: IV, oral 0.033-0.1 mg/kg/dose every 8 hr. *Children:* *Postoperative antiemetic:* IV 0.1-0.2 mg/kg/dose every 6-8 hr as needed. *Chemotherapy antiemetic:* Oral, IV 1-2 mg/kg/dose every 2-4 hr(pretreat with diphenhydramine to avoid extrapyramidal reactions). *Adults:* *Antiemetic:* Oral, IV 1-2 mg/kg/dose every 2-4 hr. *GER:* Oral 10-15 mg 4 times/day. *Renal dysfunction:* decrease dose.	*Tablet:* 10 mg. *Syrup:* 5 mg/5 ml. *Injection:* 5 mg/ml as 2 ml ampoule. *Adverse events:* Weakness, drowsiness, prolactin stimulation, diarrhea, extrapyramidal rections.
Metolazone	*Children:* 0.2-0.4 mg/kg/day in 1-2 doses. *Adults:* 2.5-20 mg/day.	*Adverse events:* Hyperglycemia, fluid and electrolyte imbalance, hypocalcemia, blood dyscrasias.
Metoprolol tartrate (Betaloc, selopress)	*Children:* Oral 1-5 mg/kg/day. *Adults:* Oral 100-450 mg/day in 2-3 doses; IV 5 mg every 2 min for 3 doses.	*Tablet:* 25, 50, 100 mg *Injection:* 1 mg/ml. *Adverse events:* Depression, bradycardia, worsen diabetes, worsen asthma, nightmares.
Metronidazole (Flagyl, metrogyl, aristogyl)	*Neonate:* 0-4 wk < 1200 g: 7.5 mg/kg PO, IV q 48 h; postnatal age ≤ 7 days 1200-2000 g: 7.5 mg/kg/day PO, IV q 24 h; > 7 days: 1200-2000 g 15 mg/kg/day PO, IV divided q 12 h; > 2000 g 30 mg/kg/day PO, IV divided q 12 h. *Children:* 30 mg/kg/day PO, IV divided q 6-8 h. *Adults:* 30 mg/kg/day PO, IV divided q 6 h. Max dose 4 g/day.	*Tablets:* 200, 400 mg. *Suspension:* 200 mg/5 ml. *Injection:* 500 mg/100 ml. *Adverse events:* Dizziness, seizures, metallic taste, nausea, disulfiram-like reaction with alcohol.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Midazolam (Mezolam, midosed)	*Neonates:* IV continuous infusion 0.15-0.5 µg/kg/min for sedation; IV bolus 0.05-0.15 mg/kg every 2-4 hr. *Infants and children:* *Status epilepticus:* IV load 0.15 mg/kg followed by continuous infusion 1-2 µg/kg/min. *Intranasal:* 2.5 mg (0.5 ml) in each naris (total 5 mg) using 5 mg/ml injection. > 12 yr: 0.5 mg every 3-4 min to effect. *Adults:* 0.5-2 mg every 2 min to effect (usually 2-5 mg).	*Injection:* 1 mg/ml. *Adverse events:* Myoclonus, sedation, amnesia, paradoxical excitation, blurred vision, diplopia, respiratory depression.
Montelukast (Singular)	*Children 6-14 yr:* 5 mg once daily in the evening. >15 yr and adults: 10 mg once daily in the evening.	*Tablets:* 5, 10 mg. *Adverse events:* Headache, dyspepsia, fatigue, elevated liver enzymes.
Morphine	*Neonates:* IV, IM, SC *Analgesia:* 0.05-0.2 mg/kg/dose every 2-4 hr; continuous infusion 0.025-0.05 mg/kg/hr. *Infants and children:* IV, IM, SC 0.1-0.2 mg/kg/dose every 2-4 hr, oral 0.2-0.5 mg/kg/dose every 4-6 hr. Adolescents > 12 yr: IV 3-4 mg, may repeat in 5 min if needed. *Adults:* Oral 10-30 mg every 4 hr or CR tablet 15-30 mg every 8-12 hr. IV, IM, SC 2.5-20 mg/dose every 2-6 hr as needed or continuous infusion 0.8-10 mg/hr.	*Injection:* 10, 15, 25 mg/ml. *Adverse events:* Physical dependence, hypotension, bradycardia, nausea, vomiting, constipation, sedation, confusion, decreased urination, respiratory depression.
Naloxone (Narcan, narcotan)	*Neonate/child:* 0.1 mg/kg IV max dose 2 mg. If no response repeat every 2-3 min until desired effect.	*Injection:* 0.4 mg/ml, 0.02 mg/ml. *Adverse events:* May precipitate acute opiate withdrawal.
Naproxen (Artagen, naprosyn)	*Child:* 5-7 mg/kg PO q 8-12 h. *Adult:* 250-375 mg PO q 8-12 h; max dose 1250 mg/day.	*Tablet:* 250 mg. *Adverse events:* GI upset, dizziness, rash, decreased renal function.
Neomycin sulfate	*Infants:* 50 mg/kg/day PO divided q 6 h. *Children:* 50-100 mg/kg/day PO divided q 6 h. *Adults:* 500-2000 mg per dose PO q 6-8 h.	*Capsule:* 350 mg. *Adverse events:* diarrhoea, rash, abdominal cramps.
Neostigmine	*Children:* 0.01-0.04 mg/kg IV, IM, SC q 2-4 h titrating dose to desired effect. To reverse non-depolarizing neuromuscular blocking agents 0.025-1 mg/kg/dose (max adult dose 5 mg).	*Tablet:* 15 mg. Injection; 0.5 mg, 2.5 mg/ml. *Adverse events:* Bradycardia, abdominal cramps, urinary frequency.
Nicotinic acid, niacin, vitamin B_3	*Deficiency (pellagra):* 50-100 mg tid to qid. *Maintenance:* 4-8 mg/1000 kcal.	*Adverse events:* Flushing, tachycardia, dizziness, hyperuricemia.
Nifedipine (Calcigard, depin)	*Infant/child: Hypertensive emergency* 0.25-0.5 mg/kg/dose PO/SL q 4-6 h (max 10 mg). *Hypertrophic cardiomyopathy:* 0.2-0.3 mg/kg PO q 8 h. *Adult:* 10 mg/dose titrated to effect (max 120-180 mg/day).	*Capsules:* 5, 10 mg. *Tablet:* 10 mg. *Depin retard capsule:* 20 mg. *Adverse events:* Hypotension, flushing, dizziness.
Nitroprusside sodium (Nipride)	*Children and adults:* 0.3-0.5 µg/kg/min titrating dose to desired effect (probable max 8 µg/kg/min).	*Injection:* 50 mg ampoule. *Adverse events:* Hypotension, tachycardia, thyroid suppression, seizures, methemoglobinemia.
Norepinephrine (Adrenor)	*Children:* 0.05-0.1 µg/kg/min titrating dose to desired effect (max dose 1 µg/kg/min).	*Adverse events:* Hypertension, arrhythmias, headache.
Nystatin (Mycostatin, nystatin)	*Premature infants:* 0.5 ml to each side of the mouth qid. *Term infants:* 1 ml to each side of mouth qid. *Children and adults:* 5000,000 U qid; administer until 48 hr after thrush has resolved. Vaginal 1-2 tablets qhs for 2 wk.	*Tablets:* 500,000 units. *Suspension:* 100,000 units/ml.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Omeprazole (Lomac, Ocid)	*Children:* 0.6-0.7 mg/kg PO qd. Dose titrated to desired gastric pH. *Adult:* 20-40 mg PO qd.	*Capsule:* 10, 20 mg. *Adverse events:* May decrease diazepam, phenytoin clearance.
Ondansetron (Emeset, periset, zofer)	*Infant/child:* 0.15 mg/kg IV q 8 h; may give as continuous IV infusion 0.45 mg/kg/day (max 24-32 mg/day) Child oral dose for mild to moderate nausea/vomiting: 4-8 mg q 8-12 h).	*Tablet:* 4, 8 mg. *Injection:* 2 mg/ml. *Adverse events:* Headache, chest pain.
Oxacillin	*Neonates:* postnatal age IM, IV ≤ 7 days: 1200-2000 g 50 mg/kg/day q 12 h; > 2000 g 75 mg/kg/day divided q 8 h; postnatal age > 7 days ≤ 1200 g: 50 mg/kg/day IV divided q 12 h; 1200-2000 g: 75mg/kg/day q 8 h; > 2000 g: 100 mg/kg/day IV divided q 6 h. *Infants:* 100-200 mg/kg/day divided q 4-6 h. *Children:* PO 50-100 mg/kg/day divided q 4-6 h. *Adults:* 2-12 g/day divided q 4-6 h (max dose 12 g/day).	*Adverse events:* Rash, eosinophilia, neutropenia.
Oxybutynin (Oxyspas, Tropan)	*Child:* 0.2 mg/kg PO q 6-12 h (max 5 mg PO q 8 h). *Adult:* 5 mg per dose up to 4 times daily.	*Tablet:* 2.5, 5 mg. *Syrup:* 2.5 mg/5 ml. *Adverse events:* Tachycardia, drowsiness, sedation, dry mouth, blurred vision.
Pancreatic enzymes	*Enteric coated:*1-2 capsules with meals, I capsule with snacks. *Non-enteric coated:* 3-12 tablets or 1-4 teaspoon powder with each meal; titrate according to patient's need.	*Adverse events:* Rash, abdominal complaints, constipation, hyperuricemia, allergy.
Pancuronium (Pavulon)	*Children and adults:* 0.04-0.1 mg/kg IV q20-30 min. Dose titrated to desired effects.	*Injection:* 2 mg/ml, 1 mg/ml. *Adverse events:* Tachycardia, hypertension, prolonged muscle weakness.
Paraldehyde	*Children:* 0.15 ml/kg/dose PO, PR. May repeat once in 4-6 hr. *Adults:* 5-10 ml/dose.	*Injection:* 5 ml ampoule, 1 gm/ml. *Adverse events:* Sedation, GI irritation, thrombophlebitis.
Pantoprazole (Pantocid)	*Adult:* 40 mg qd.	*Tablet:* 20, 40 mg *Injection:* 40 mg/vial.
Penicillamine	*Wilson disease:* Dose titrated to maintain > 1 mg/day urinary copper excretion. *Infant and child:* 20 mg/kg/day PO q 6-12 h (max 1 g/day). *Adult:* 1 g/day PO q 6-12 h (max 2 g). *Lead intoxication:* *Infant/child:* 30-40 mg/kg/day PO q 8-12 h (max 1.5 g/day) *Adult:* 1-1.5 g/day PO q 8-12 h. *Rhematoid arthritis* *Children:* 3 mg/kg/day PO q 12 hr, increasing by 3 mg/kg/day every 2-3 mo to max 10 mg/kg/day.	*Adverse events:* Rash, pruritis, nausea, vomiting, anemia, bone marrow suppression, nephrotic syndrome, SLE-like syndrome.
Penicillin G preparations, potassium, sodium (Benzyl penicillin, Pentid)	*Neonates:* postnatal age IM, IV ≤ 7 days: 1200-2000 g 50,000 units/kg/day q 12 h (meningitis 100,000 units/kg/day divided q 12 h); > 2000 g: 75000 units/kg/day divided q 8 h (meningitis 1,50,000 units/kg/day IV divided q 8 h); postnatal age > 7 days < 1200 g; 50,000 units/kg/day IV divided q 12 h (meningitis 100,000 units/kg/day divided q 12 h); 1200-2000 g: 75,000 units/kg/day q 8 h (meningitis 125,000 units/kg/day divided q 8 h): > 2000 g: 100,000 units/kg/day IV divided q 6 h (meningitis 200,000 units/kg/day divided q 6 h). *Children:* 100,000-250, 000 units/kg/day IV, IM divided q 4-6 h (up to 400,000 units/kg/day). *Adults:* 2-24 million units/day IM, IV divided q 4-6 h.	*Injection:* 5,00,000-10,00,000 units/vial. *Tablet:* 2,00,000 units (125 mg). *Adverse events:* Rash, anaphylaxis, seizures, eosinophilia.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Penicillin benzathine (Penidure LA 6, LA 12, LA 24)	*Neonates:* >1200 g 50, 000 units/kg once IM. *Children:* 300,000-1.2 million units/kg IM once every 3-4 wk, max 1.2-2.4 million units/dose. *Adults:* 1.2 million units IM every 3-4 wk.	*Injection:* 0.6, 1.2, 2.4 million/vial. *Adverse events:* Rash, eosinophilia, allergy.
Penicillin G procaine	Neonates > 1200 g 50, 000 units/kg IM qd. *Children:* 25,000-50,000 units/kg IM qd for 10 days; max 4.8 million units per dose. *Gonorrhea:* 100, 000 units/kg (max 4.8 million units/day) once with probenicid 25 mg/kg (max dose 1 g). *Adults:* 0.6-4.8 million units IM q 12-24 h.	*Injection:* 4,00,000 units/vial. *Adverse events:* Rash, allergic reactions, eosinophilia.
Penicillin V (Penivoral)	*Children:* 25-50 mg/kg/day PO divided q 4-8 h. *Adults:* 125-500 mg PO q 6-8 h (max dose 3 g/day).	*Tablets:* 55, 125, 130, 250 mg. *Adverse events:* Allergy, seizures, rash, eosinophilia.
Pentamidine isothionate (Pentacarinate)	*Pneumocystis carnii pneumonia treatment* 4 mg/kg/day IM or IV for 21 days. *Pneumocystis carnii prophylaxis* 4 mg/kg/dose IM, IV every 2-4 wk. Aerosol once/mo using Respigard II nebulizer. *Infant:* use dose formula (2.27 mg/kg pentamidine) × (nebulizer output L/min) × patient body weight (Kg) divided by alveolar ventilation (L/min). Child > 5 yr: 300 mg per dose every 4 week. *Adult:* 300 mg every 4 week.	*Injection:* 300 mg/vial. *Adverse events:* Hypotension, tachycardia, hypoglycaemia, nephrotoxicity, bronchospasm, marrow suppression.
Pentobarbitone	*Sedation* *Children:* 2-6 mg/kg/day PO, IM q 6 h. May give rectally dosed by body weight: 4.5-10 kg 30 mg; 10-18 kg, 18-36 kg 60 mg; 36-50 kg 60-120 mg. *Pentobarbital coma* Children; Loading dose 10-15 mg/kg IV slowly over 1-2 hr monitoring blood pressure and heart rate. Maintenance infusion 1 mg/kg/hr increasing up to 5 mg/kg/hr to maintain burst suppression on EEG.	*Adverse events:* Arrhythmias, bradycardia, hypotension, respiratory depression, laryngospasm, dependence.
Phenobarbitone sodium (Gardenal, luminal)	Anticonvulsant loading dose *Children and adults:* 15-20 mg/kg PO, IV. *Maintenance dose* *Neonates:* 3-4 mg/kg/day PO, IV q 12-24 h. *Children:* 5-6 mg/kg/day PO, IV q 12-24 h. *Adults:* 1-3 mg/kg/day PO, IV q 12-24 h. *Sedation* *Children:* 2 mg/kg/dose. *Hyperbilirubinemia* *Children:* 3-8 mg/kg/day PO, IV q 12-24 hr. *Adult:* 90-180 mg/day PO, IV q 12-24 hr.	*Tablets:* 30, 60 100 mg. *Syrup:* 20 mg/5 ml. *Injection:* 200 mg/ml. *Adverse events:* Hypotension, drowsi ness, respiratory depression, paradoxical hyperactivity.
Phenoxybenzamine	*Children:* 0.2-2 mg/kg/day PO qd. Titrate dose to desired effect. *Adult:* 10 mg/dose PO q 12 h titrate dose to effect.	*Adverse events:* Postural hypotension, syncope, dizziness.
Phentolamine	*Pheochromocytoma* *Diagnosis:* *Child:* 0.05-0.1 mg/kg/dose; usual max dose 5 mg. *Adult:* 5 mg per dose. *Preoperatively:* *Children:* 0.05-0.1 mg/kg/dose every 1-2 hr titrating to effect and needed duration. Usual max dose 5 mg.	*Adverse events:* Hypotension, dizziness, gastritis.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	Extravasation 5-10 mg in 10 ml 0.95 normal saline–infiltrate area with small volume using 27-30 gauge needle not to exceed total dose of 0.1 mg/kg.	
Phenylephrine (Drosyn eye drops, Penrex)	Nasal decongestant *Infants*: 1-2 drops per nare q3-4h 0.16% solution. *Children 1-6 yr*: 1-2 drops/spray per nare q 3-4 h 0.125% solution. *6-12 yr*: 1-2 drops/spray q 3-4 h 0.25% solution. *>12 yr/adult*: 1-2 drops/spray per nare q 3-4 h 0.25-0.5% solution. *Hypotension/shock* *Children*: 5-20 µg/kg per dose IV q 10-15 min. May give by continuous IV infusion 0.1-0.5 µg/kg/min titrated to desired effects. *Adults*: 0.1-0.5 mg/dose q 10-15 min continuous IV infusion 100-180 µg/min titrating to desired effect. Paroxysmal supraventricular tachycardia *Children*: 5-10 µg/KG IV over 20-30 seconds. *Adults*: 0.25-0.5 mg IV over 20-30 sec.	*Eye drops:* 5, 10%. *Adverse events:* Hypertension, angina, bradycardia, restlessness, necrosis if IV infiltrates.
Phenytoin (Dilantin, epsolin)	*Status epilepticus:* loading dose *Neonate:* 15-20 mg/kg IV; do not exceed 0.5 kg/min. *Child/adult:* 15-18 mg/kg IV; do not exceed 1-3 mg/kg/min. *Maintenance dose* *Neonate:* 5 mg/kg/day PO, IV q 12-24 h. *Children:* 0.5-6 yr: 8-10 mg/kg/day. 7-9 yr: 6-8 mg/kg/day PO, IV q 12-24 h. 10-16 yr: 6-7 mg/kg/day PO, IV q 12-24 h. *Adult:* 300-600 mg/day q 12-24 h. Arrhythmias: loading dose Child/adult: 1.25 mg/kg IV q 5 min until desired effect or total dose 15 mg/kg. *Maintenance dose* *Child:* 5-10 mg/kg/day q 8-12 h. *Adult:* 250 mg per dose q 6-8 h.	*Tablet:* 50,100 mg. *Syrup:* 30,125 mg/5 ml. *Injection:* 50 mg/ml, 2 ml ampoule. *Adverse events:* Lethargy, dizziness, nystagmus, hypotension, hirsutism, gingival hyperplasia, rash, Steven-Johnson syndrome, hepatitis, thrombophlebitis. Phenytoin therapeutic concentration: 8-20 µg/ml.
Physostigmine	*Children:* 0.001-0.03 mg/kg/dose IM, IV, SQ, repeated q 15-20 min to desired effect (max total dose 2 mg). *Adults:* 0.5-2 mg IM, IV, SQ repeated q 15-20 min until desired effect.	*Adverse events:* Palpitations, restlessness, excessive salivation, secretions, muscle fasciculations, bronchospasm.
Phytonadione (Vitamin K1)	*Children:* 1-2 mg/dose IM, IV, SQ dosed to effect; PO dose may increase to 2.5 to 5 mg. *Adults:* 10 mg/day IM, IV< SQ; 5-25 mg/day PO, higher doses may be required for reversal of warfarin like anticoagulant toxicity.	*Adverse events:* Flushing, hypotension.
Piperacillin (Piperapen, piperacil)	*Neonates:* postnatal age ≤ 7 days 150 mg/kg/day IV divided q 8-12 h; > 7 days: 200 mg/kg/day divided q 6-8 h. *Children:* 200-300 mg/kg/day divided q 4-6 h; Cystic fibrosis 350-500 mg/kg/day IV. *Adults:* 2-4 g/dose IV q 4-6 h (max dose 24g/day).	*Injection:* 1, 2, 4 g/vials. *Adverse events:* Rash, eosinophilia, serum sickness like reaction, increase in liver enzymes.

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Generic name (Trade name)	*Dose/Route of administration*	*How supplied/Major side effects*
Piperacillin-Tazobactam (Tazin, Zosyn)	*Children:* 300-400 mg/kg/day IM, IV q 6-8 h. *Adults:* 3.375 g IM, IV q 6-8 h.	*Adverse events:* Rash, eosinophilia, increase in liver enzymes.
Potassium chloride (Potklor, keylyte)	1-2 mEq/kg/day q 8 h.	*Syrup:* 20 mEq/15 ml *Injection:* 2 mEq/ml, 10 ml ampoule.
Pralidoxime (Neopam)	*Children:* 20-50 mg/kg/dose IM, IV repeated in 1-2 hr if muscle weakness has not been relieved; when desired effect obtained dose q 12 h. *Adults:* 1-2 g IM, IV q5-6 h dose based on clinical response.	*Injection:* 500 mg/20 ml. *Adverse events:* Hypertension, dizziness, nausea, muscle weakness/rigidity.
Prazosin (Minipress XL, Prazopress)	*Child*: 0.1 mg/kg/day PO q 6 h titrating dose to desired blood pressure. Usual max dose 0.4 mg/kg/day or 15 mg total dose. Consider additive/synergistic combinations with diuretics. *Adult*: 3 mg/day PO q 8-12 h titrating dose to desired blood pressure. Usual dose range 3-15 mg/day.	*Tablets:* 1, 2, 2.5, 5 mg. *Adverse events:* Syncope, palpitations, dizziness, fluid retention.
Prednisone (Wysolone, deltacortil)	*Asthma* *Children:* 0.5-4 mg/kg/day PO, IV q 6-12 h. *Adult:* 5-60 mg/day PO, IV. *Anti-inflammatory* *Children:* 0.1-2 mg/kg/day PO, IV q 6-q day.	*Tablets:* 5, 10, 20 mg. *Adverse events:* Edema, hypertension, psychosis, cushing's syndrome, peptic ulcer, HPA axis suppression.
Primaquine phosphate (Malirid)	*Child:* 0.3 mg base/kg/day PO once daily for 14 days (max daily dose 15 mg). *Adult:* 15 mg PO once daily for 14 days.	*Tablets:* 7.5, 15 mg. *Adverse events:* Pruritis, anemia, methemoglobinemia.
Procainamide (Pronestyl)	*Loading dose* *Child*: 3-6 mg/kg/dose IV over 5 min not to exceed 100 mg/dose; repeat q5-10 min as needed to max 15 mg/kg total dose. Do not exceed 500 mg in 30 min. *Maintenance dose* *Child*: 15-50 mg/kg/day PO q 3-6 h; 20-30 mg/kg/day IM, IV; not to exceed 4 g/day; continuous IV infusion 20-80 μg/kg/min, usual max 2 g/day. *Adult*: 250-500 mg/dose q 3-6 h, max 2-4 g/day.	*Tablet:* 250 mg. *Injection:* 100 mg/ml. *Adverse events:* Hypotension, arrhythmias, A-V block, confusion, agranulocytosis, SLE- like syndrome, fever, rash.
Prochlorperazine (Stemetil, Protil)	*Child:* 0.4 mg/kg/day PO, rectal q 6-8 h; 0.1-0.15 mg/kg/day IM q 8-12 h. *Adult:* 5-10 mg/dose, PO 3-4 times daily.	*Tablets:* 5, 25 mg. *Injection:* 12.5 mg/ml, 1 ml ampoule, 10 ml vial.
Promethazine (Phenergan, promet)	*Motion sickness* *Child:* 0.5 mg/kg PO, 30-60 min before departure then q 8-12 as needed. *Sedation-antiemetic* *Child:* 0.25-1 mg/kg/dose IM, IV, rectal q 4-6 h as needed.	*Tablet:* 10, 25 mg. *Syrup:* 5 mg/ml. *Injection:* 25 mg/ml, 2 ml ampoule. *Adverse events:* Sedation, hypotension, extrapyramidal reactions, blurred vision.
Propofol (Profol, propovan)	*Sedation* *Child:* 1.5-3 mg/kg/dose IV over 1-2 min. *Continuous sedation* (mechanical ventilation) *Children:* 5.5 mg/kg for 30 min; increase to 6 mg/kg for 30 min; increase to 8 mg/kg for 1 hour; increase to 10 mg/kg for 1 hour; increase to final infusion rate of 12.5 mg/kg/hr.	*Injection:* 10 mg/ml. *Adverse events:* Hypotension, bradycardia, hyperlipidemia, questionable metabolic acidosis.
Propanolol (Ciplar, Inderal)	*Neonate:* 0.25 mg/kg/dose PO q 6-8 h; titrate to desired response increasing dose slowly; max dose 5 mg/kg/day. IV dose: 0.01 mg/kg over 10-15 min titrate to desired effect; max dose 1 mg/kg/day. *Arrhythmias/hypertension* *Children:* 0.5-1 mg/kg/day PO q 6-8 h titrated upward to 2-5 mg/kg/hour, over 3-5 days.	*Tablets:* 10, 40, 80 mg. *Injection:* 1 mg/ml. *Adverse events:* Decreased cardiac contractility, hypotension, bradycardia, hypoglycaemia, bronchospasm.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	IV dose: 0.01-0.1 mg/kg/dose infused over 10-15 min as needed (max dose 1 mg infants, 3 mg children). *Adults:* 40-80 mg/day, titrating to response; range 40-320 mg/day PO q 6-8 h. *Thyrotoxicosis* *Neonate:* 2 mg/kg/day Po q 6-8 h; titrate to response. *Children:* 2-4 mg/kg/day Po q 6-8 h; titrate to response. *Migraine prophylaxis* *Children:* 0.6-2 mg/kg/day PO q 6-8 h; usual max 4 mg/kg/day.	
Propylthiouracil	*Neonate:* 5-10 mg/kg/day PO q 8 h titrate to effect. *Children:* 5-7 mg/kg/day PO q 8 h titrate to effect. *Adult:* 300-450 mg/day PO q 8 h increasing to 600-1200 mg/day.	*Tablet:* 50 mg. *Adverse events:* Vertigo, skin rash, blood dyscrasia, hepatitis, arthralgia, interstitial pnemonitis.
Prostaglandin E1, PGE1 (Prostin VR, alprostadil)	*Neonates* *Initial:* 0.05 µg/kg/min; advance to 0.4 µg/kg/min. *Maintenance:* When increase in PO_2 is noted, decrease to lowest effective dose.	Injection: 500 µg/ml.
Protamine sulphate (Prota)	1 mg protamine neutralizes 90 USP units of lung derived heparin and 115 USP units of intestinal derived heparin. Protamine dose calculated on duration of time since last heparin dose using heparin elimination half life (~1 hr) to determine estimated heparin body stores.	*Injection:* 10 mg/ml *Adverse events:* Hypotension, dyspnoea, hypersensitivity.
Protein C (Activated) (XYGRIS)	*Severe Sepsis* 24 microgram/kg/HR for 96 hours Limited pediatric studies. May use in teenagers	*Adverse effects:* Bleeding Contraindicated in patients with DIC with active bleeding.
Pseudoephedrine (Sudafed)	*Infant/child:* 4 mg/kg/day PO, q 6-12 h. *Adult:* 60 mg/dose PO, q 6-8 h; max 240 mg/day.	*Tablet:* 60 mg. *Syrup:* 30 mg/5 ml. *Adverse events:* Tachycardia, headache, nervousness, tremor.
Pyrazinamide (Pyzina, PZA-CIBA)	*Children:* 15-40 mg/kg/day PO divided q 12-24 h (max dose 2 g/day). *Adult:* 15-30 mg/kg/day PO divided q 6-24 h.	*Tablets:* 250, 300, 500, 750 mg. *Syrup:* 250 mg/ml. *Adverse events:* Photosensitivity, GI upset hyperuricemia, arthralgia, hyporoxicity.
Pyridostigmine (Mestinon)	*Myasthenia gravis* *Children*: 0.05-0.15 mg/kg/dose IM, IV; max dose 10 mg titrate to effect; PO dose 7 mg/kg/day in 5-6 divided doses. *Adult*: 2 mg IM, IV q 2-3 h; PO dose 60 mg per dose q 8 h; titrate dose to desired effect. *Reversal of neuromuscular blocking agents* *Children*: 0.1-0.25 mg/kg/dose IM, IV titrate to effect; may need to co-administer with atropine/glycopyrrolate. *Adult*: 10-20 mg per dose with atropine/glycopyrrolate.	*Tablet:* 60 mg. *Adverse events:* Bradycardia, A-V block, seizures, headache, diarrhoea, urinary frequency, muscle weakness, miosis, abdominal cramping, lacrimation, increased bronchial secretions.
Pyridoxine, vitamin B_6 (Benadon, bevidox, pyricontin)	*Pyridoxine dependent seizures* *Children:* 50-100 mg PO, IM, IV; maintenance dose 50-100 mg/day. *Dietary deficiency* *Children:* 5-15 mg/day for 3-4 wk then 2.5-5 mg/day. *Adults:* 10-20 mg/day for 3-4 wk. *Drug induced neuritis* *Children:* 1 mg/kg/day PO, IM, IV q day. *Adult:* 100-200 mg/day PO, IM, IV q day.	*Tablets:* 40, 100 mg. *Injection:* 100 mg/ml. *Adverse events:* Nausea, decreased folic acid, increased liver function tests, nausea.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Pyrimethamine (Daraprim)	*Malarial prophylaxis:* begin drug 2 wk before entering endemic areas.	
Pyrimethamine and Sulphadoxine (Reziz, laridox)	*Child:* 0.5 mg/kg once a wk (max dose 25 mg). Chloroquine resistant malaria (with quinine and sulfa). *Toxoplasmosis (with sulfadiazine)*	
Pyrimethamine and sulphamethopyrazine (Metakefin)	*Children:* 2 mg/kg/day PO divided q 12 h for 2-3 days then 1 mg/kg/day PO qd with sulfadiazine for 6 mo then 1 mg/kg/day PO qd 3 times/wk max daily dose 25 mg/day. *Adult:* 50-75 mg plus 1-4 g sulfadiazine PO 3 times/wk. *Toxoplasma gondii prophylaxis* Infant > 1 month: 1 mg/kg/day PO qd plus dapsone. Adolescents/adults: 50 mg PO once weekly plus dapsone. *Pnemocystis carinii prophylaxis* Adolescent/adult: 50-75 mg PO once week plus dapsone.	*Tablet:* 25 mg *Reziz:* 25 + 500. *Metakefin:* 25 + 500. *Adverse events:* seizures, headache, photosensitivity, rash, marrow suppression, tremor, folic acid deficiency.
Ranitidine (Histac, Rantid, Aciloc)	*Neonate:* 1.5-2 mg/kg/day PO, IV q 12 h; continuous 24 hr IV infusion 0.04 mg/kg/hr max 1 mg/kg/day. *Children:* 1-5 mg/kg/day PO, IM, IV q 6-8 h; continuous 24hr IV infusion 2-5 mg/kg/day. *Adults:* 150 mg/dose PO q 12 h or 300 mg PO qhs; 50-100 mg/dose IM, IV q 6-8 h.	Tablet: 150, 300 mg. Injection: 50 mg/2 ml. *Adverse events:* Headache, mental confusion, pain at injection site.
Ribavarin	*Children and adults:* use SPAG-2 small particle generator at 20 mg/ml concentration for continuous aerosolization 12-18 hr per day.	Capsule: 100, 200 mg. *Adverse events:* rash, irritation, hypotension.
Riboflavin, vitamin B2 (Lipobal)	*Deficiency:* *Children:* 2.5-10 mg/day PO, q 8-12 h. *Adults:* 5-30 mg/day PO, q 8-12 h.	*Tablet:* 20 mg.
Rifampicin (R-cin, rifampin)	*Children:* 10-20 mg/kg/day PO, IV divided q 12-24 h. *Adult:* 10 mg/kg/day PO, IV once daily; max dose 600 mg/day.	*Capsule:* 150, 300 mg. *Syrup:* 100 mg/5 ml. *Adverse events:* Hepatotoxicity, flu like syndrome, rash, pruritits, leukopenia, arthralgia.
Salmeterol (Serobid, salmeter)	*Child/adult:* 1 (21 µg)-2 puffs, aerosol q 12 h titrate to desired effect.	*Inhaler:* 25 µg/metered dose. Rotacaps: 50 µg. *Adverse events:* Tachycardia, palpitations, headache, nervousness, muscle tremor, cough, airway irritation.
Scopolamine	*Postoperative emesis* *Children:* 6 µg/kg/dose IM, IV, SC q 6-8 h. *Adult:* 0.3-0.65 mg/dose IM, IV SC q 6-8 h. *Motion sickness* *Children and adults:* One patch behind the ear at least 4 hr before movement.	*Adverse events:* Tachycardia, disorientation, sedation, psychosis, dry mouth, constipation, urinary retention, blurred vision.
Selenium	Deficiency *Children:* 3 µg/kg/day. *Adults:* 150-400 mg/day.	
Selenium sulphide (Seldruff, Selsun)	*Tinea capitis:* Apply twice weekly for 2-4 wk. *Tinea versicolor:* Apply once weekly for 4 wk; 2.5% lotion may be applied daily for 7 days; lather and rinse from body areas after 5 min or from face after 10 min; avoid eyes and genital areas.	*Satchet:* 2.5% *Suspension:* 2.5% w/v 60, 120 ml.
Simethicone	*Children < 2 yr:* 20 mg/dose PO q 4-6 h. *Children 2-12 yr:* 40 mg/dose q 6 h.	

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	Children >12 yr and adults: 40-120 mg PO q 6 h, dose titrated to effect.	
Sodium polysterene sulphonate (Kayexalate, SPS)	Children: 4 g/kg/day PO, q 4-8 h; Rectal: 4-12 g/kg/day PR q 2-6 h. *Adults:* 15 g/dose PO, q 6-12 h.	*Adverse events:* Abdominal cramping, bloating, hypokalemia.
Spironolactone (Aldactone, lactone)	*Neonates*: 1-3 mg/kg/day PO divided q 12-24 h. *Children:* 1.5-3.3 mg/kg/day PO divided q 8-24 h. *Adults:* 25-200 mg per dose PO q 12-24 h.	*Tablet:* 25, 100 mg. *Adverse events:* Lethargy, hyperkalemia, gynecomastia, nausea, rash.
Streptokinase (Eskinase, streptase, thrombosolv)	*Thrombosis* 3500-4000 units infused IV over 30 min followed by 1000-1500 units IV continuous infusion. *Clotted catheter* 10,000-25000 units in normal saline the volume of the catheter instilled into catheter for ~ 1 hr, then removed (aspirated).	*Injection:* 7,50,000 iu, 15,00,000 iu/vial. *Adverse events:* Bleeding, bronchospasm, flushing, rash.
Streptomycin	*Neonate:* 10-20 mg/kg/day IM qd. *Children:* 20-40 mg/kg/day IM divided q 12 h not to exceed 1 g/day. *Adults:* 15 mg/kg/day IM qd, not to exceed 1 g/day.	*Injection:* 0.75, 1 gm/vial. *Adverse events:* Ototoxicity, nephrotoxicity
Succinylcholine (Entubate, scoline)	*Children:* 1-2 mg IV initial dose; maintenance 0.3-0.6 mg/kg IV q 5-10 min dose titrated to level of skeletal muscle relaxation. *Adults:* 0.6 mg/kg up to 150 mg IV initial dose; maintenance 0.04-0.07 mg/kg IV q 5-10 min titrated to effect.	*Injection:* 50 mg/ml, 500 mg/vial. *Adverse events:* Bradycardia, hypotension, malignant hyperthermia, hyperkalemia, bronchospasm.
Sucralfate (Mucogard, sucral)	*Children:* 40-80 mg/kg/day PO divided q 6-8 h. Stomatitis 5-10 ml swish/spit or swallow q 6 h. *Adults:* 1 g per dose PO q 4-6 h.	*Tablet:* 1 gm. *Suspension:* 1 gm/10 ml. *Adverse events:* Headache, constipation, abdominal cramping, rash.
Sulfadiazine	*Toxoplasmosis:* Neonates: 100 mg/kg/day PO divided q 12 h with pyrimethamine 1 mg/kg/day PO qd (with folinic acid). *Children:* 120-200 mg/kg/day PO divided q 6 h with pyrimethamine 2 mg/kg/day PO divided q 12 h for 3 days then 1 mg/kg/day (max dose 25 mg/day) with folinic acid. *Rheumatic fever prophylaxis* ≤ 30 kg 500 mg/day; > 30 kg 1 g/day PO qd.	*Adverse events:* Rash, steven-johnson syndrome, nausea, leucopenia, crystalluria.
Sulfasalazine (Sazo-en)	Children: initial 40-75 mg/kg/day PO divided q 4-6 h not to exceed 6g/day; maintenance 30-50 mg/kg/day PO divided q 6-8 h. *Adults:* 1 g per dose PO q 6-8 h; max dose 6 g/day.	*Tablet:* 500 mg. *Adverse events:* Rash, dizziness, headache, nausea, bone marrow suppression.
Sulfasoxazole	*Children:* 120-150 mg/kg/day PO divided q 4-6 h (max dose 6 g/day). *Adults:* 4-8 g/day PO divided q 4-6 h.	*Adverse effects*: Rash, Steven-Johnson syndrome, nausea, leucopenia, crystalluria.
Tacrolimus	*Children:* Oral 0.15 mg/kg every 12 hrs; IV continuous infusion 0.05-0.1 mg/kg/day. *Adults:* Oral 0.075-0.15 mg/kg every 12 hr; IV continuous infusion 0.05-0.1 mg/kg/day.	*Adverse effects:* Hypertension, hypo-hyperkalemia, hyperglycemia, liver damage, nephrotoxicity, pleural effusion, edema
Teicoplanin (Targocid)	*Neonates:* Loading dose 16 mg/kg on day 1, then maintenance 8 mg/kg qd. *Children:* 10 mg/kg every 12 hrs for 3 doses then 6 mg/kg IV, IM qd.	*Injection:* 200, 400 mg/vials. *Adverse effects:* Erythema, thrombophlebitis, increase in liver enzymes, dizziness, bronchospasm.

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
Terbutaline (Bricanyl, asmaterb, bromenyl)	*Children < 12 yr:* Oral 0.05 mg/kg/dose (max 5 mg) every 8 hr. SC 0.005-0.01 mg/kg/dose (mx 0.4 mg), may repeat in 15-20 min. *Children >12 yr and adults:* Oral 2.5-5 mg/dose every 6-8 hr SC 0.25 mg/dose, may repeat in 15 min. *Children and adults:* MDI 1-2 puffs every 6-8 hr as needed.	*Tablet:* 2.5, 5 mg. *Syrup:* 1.5 mg/5 ml. *Injection:* 0.5 mg/ml. *Misthaler:* 250 µg/metered dose. *Nebulizing solution:* 10 mg/ml. *Adverse events:* Tachycardia, arrythmias, flushing, headache, nervousness, tremor, hypokalemia, muscle cramps, paradoxical bronchospasm.
Terfenadine (Rhiter, terfed, zoter)	*Children*: 3-6 yr: 15 mg twice daily. 6-12 yr: 30 mg twice daily. > 12 yr and adults: 60 mg twice/day.	*Tablet:* 60, 120 mg. *Syrup:* 30 mg/5 ml. *Adverse events:* Drowsiness, fatigue, arrhythmias.
Testosterone (Depot-Testosterone) (Aquaviron, testanon)	*Children:* IM *Male hypogonadism:* Initiation of prepubertal growth and delayed puberty: 40-50 mg/m2/dose monthly; *Terminal growth phase:* 100 mg/m2/dose twice mo. *Adults:* *Hypogonadism:* IM 50-400 mg every 2-4 wk.	*Injection:* 25, 30, 50 mg/ml. *Depot injection:* 250 mg/ml. *Adverse events*: Acne, bladder irritability, aggressive behavior, depression, sleeplessness, headache, hirsutism, hepatic dysfunction.
Tetanus antitoxin (Tetanus antitoxin Bengal immunity, Haffkine)	*Children and adults:* SC, IM *Prophylaxis* <30 kg 1500 units; >30 kg 3000-5000 units *Treatment:* inject 10,000-40,000 units into wound and 40,000-10,000 units IV.	*Injection:* 750, 1500, 5000, 10,000, 20,000, 50,000 iu/5-10 ml ampoule. *Adverse events:* Serum sickness, urticaria, skin eruptions, allergic reactions.
Tetanus immune globulin (Tetglob)	*Prophylaxis:* *Children:* 4 units/kg. *Adults:* 250 units IM. *Treatment:* *Children:* 500-3000 units. *Adults:* 3000-6000 units (infiltrate the some of the dose around wound).	*Injection:* 250 units/2 ml. *Adverse events:* Allergic reactions.
Theophylline (Broncordil, deriphyllin)	*Neonates:* Apnea, bronchodilation: Loading dose 6-10 mg/kg, maintenance dose 2-4 mg/kg/dose every 12 hr. *Infants and children:* 6 wk-6 mo: 10 mg/kg/day. 6 mo-1 yr: 12-18 mg/kg/day. 1-9 yr: 20-24 mg/kg/day. 9-12 yr: 16 mg/kg/day. 12-16 yr: 13 mg/kg/day. *Adults:* 10 mg/kg/day. (Dosing may be increased for smokers and enzyme inducing drugs; decrease dose if enzyme inhibitors, liver disease, heart failure or hypothyroid).	*Tablets:* 77 + 23, 250 mg. *Retard tablet:* 150, 300, 450 mg. *Suspension:* 80 mg/15 ml, 46.5 + 14 mg/5 ml. *Injection:* 169.4 + 50.6/2 ml. *Adverse events:* Tachycardia, nervousness, hyperactivity, irritability, headache, seizure, arrhythmias, nausea, vomiting, frequent urination.
Thiamine, vitamin B1 (Benalgis, beneuron)	*Beriberi:* *Children:* IM, IV 10-25 mg/day or oral 10-50 mg/day for 2 wk, then 5-10 mg/day for 1 mo. *Adults:* IM, IV 5-30 mg 3 times daily for 2 wk, then oral 5-30 mg/day for 1 mo. *Wernicke:* IM, IV 100 mg/day until consuming a balanced diet.	*Tablet:* 75 mg *Capsule:* 5 mg. *Injection:* 100 mg/ml. *Adverse events*: Cardiovascular collapse with repeated IV doses, angioedema, rash, tingling.
Thiopental sodium (Pentothal, thiosol)	*Neonates: Anesthesia:* 3-4 mg/kg; *Seizures:* 2-3 mg/kg IV, repeat doses 1 mg/kg as needed.	*Injections:* 250, 500 mg, 1 gm/vials. *Adverse events:* Cramping, diarrhea,

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Generic name (Trade name)	Dose/Route of administration	How supplied/Major side effects
	Infants and children: IV *anesthesia:* 5-8 mg/kg; seizures 2-3 mg/kg; *increased ICP:* 5 mg/kg repeated as needed. *Adults:* IV 25-250 mg as needed for effect. *Sedation:* Rectal *Children:* 5-10 mg/kg/dose. *Adults:* 3-4 g/dose.	rectal bleeding, hypotension, myocardial depression, emergence delirium, respiratory depression, coughing, bronchospasm, laryngospasm, hiccups, sneezing.
Ticarcillin (Ticar)	*Neonates:* postnatal age ≤ 7 days < 2000 g: 150 mg/kg/day IV divided q 8-12 h; >2000 g: 225 mg/kg/day IV divided q 8 h.; > 7days < 1200 g: 150 mg/kg/day divided q 12 h; 1200-2000 g: 225 mg/kg/day divided q 8 h, > 2000 g: 300 mg/kg/day IV divided q 6-8 h. *Children:* 200-400 mg/kg/day divided q 4-6 h; *Cystic* fibrosis 400-600 mg/kg/day IV. *Adults:* 2-4 g/dose IV q 4-6 h (max dose 24 g/day).	*Injections:* 1, 3, 5 g/vial. *Adverse events*: Rash, eosinophilia, interferes with platelet aggregation, increase-in liver enzymes.
Ticarcillin and clavulanate (Timentin)	*Children:* 280-400 mg/kg/day IM, IV q 4-8 h. *Adults:* 3.1 g IM, IV q 4-8 h (max dose 18-24 g/day).	*Injection:* 3 + 100 mg/vial. *Adverse events*: Rash, eosinophilia, increase in liver enzymes.
Tigecycline	Tygacil is administered via intravenous infusions over 30 to 60 minutes. The initial dose is 100 mg followed by 50 mg every 12 hours The usual duration of treatment is 5-14 days.	Single dose vial: 5 ml; 50 mg power for reconstitution Adverse effects: Nausea, Vomiting, diarrhea, pain at injection site hepatotoxic
Tobramycin (Tobramin, tobraneg)	*Neonates:* IM, IV (over 30-60 min): Postnatal age ≤ 7 days, 1200-2000 g: 2.5 mg/kg q 12-18 h; > 2000 g: 2.5 mg/kg q 12 h; postnatal age>7 days 1200-2000 g 2.5 mg/kg q 8-12 h; >2000g; 2.5 mg/kg q 8 h. *Children:* 2.5 mg/kg/day divided q 8-12 h. alternatively may administer 5-7.5 mg/kg/day IV qd. Preservative free preparation for intraventricular or intrathecal use: Neonate 1 mg/day; child 1-2 mg/day; adult 4-8 mg/day. *Adults:* 3-6 mg/kg/day divided q 8 h.	*Injections:* 10, 20, 40, 60, 80 mg/vial. *Adverse events*: Ototoxicity, nephrotoxicity.
Tocopherol, vitamin E (Evion)	*Premature infants (maintenance):* 25, 50 IU/day until 6-10 wk of age. Patients with persistent cholestasis: 50-400 IU/day.	*Pearls:* 30, 200, 400, 600 mg *Drops:* 50 mg/ml.
Trichlofos (Pedichloryl)	20 mg/kg/dose	*Syrup:* 500 mg/5 ml.
Triretoin, retinoic acid, vitamin A	*Children > 12 yr:* Apply weaker formulation once daily at bedtime. Increase as needed.	*Adverse events:* Excessive dryness, erythema, scaling, photosensitivity.
Triamcinolone (Kenacort, kenalog)	*Children 6-12 yr:* IM 0.03-0.2 mg/kg every 1-7 days. MDI 2 puffs 2-4 times a day. *Intranasal:* 1 spray in each nostril once daily 1-2 times/day. *Injection:* intraarticular, intrabursal, or tendon sheath 2.5-15 mg (repeat as needed). Children > 12 yr and adults: MDI 2-4 puffs 2-4 times/day; intranasal: 2 sprays in each nostril once daily (max 4 sprays/day). Intra-articular, intrasynovial; 2.5-40 mg; Oral: 40-100 mg/day in 1-4 doses; Topical: Apply thin film 2-3 times daily.	*Tablet:* 4 mg. *Injection:* 10, 40 mg/ml. *Adverse events*: skin, atrophy, cataracts, osteoporosis, oral candidiasis, fatigue.
Trimethoprim	*Children:* for UTI 4-6 mg/kg/day PO divided q 12 h >12 yr and adult: 100-200 mg PO q 12 h. *Pnemocystis carnii* pneumonia (with dapsone): 15-20 mg/kg/day PO q 6 h for 21 days.	*Adverse events*: Megaloblastic anemia, bone marrow suppression, nausea, epigastric distress, rash.
Tromethamine (Tham)	Neonates, infants, children and adults: Dose (ml of 0.3 M solution) = weight (kg) × base deficit; or 1-2 mEq/kg/dose.	*Adverse events*: Apnea, hypoglycemia, hyperkalemia, tissue irritation, necrosis if direct contact.

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Generic name (Trade name)	Dose/Route of administration	[illegible]
Tropicamide (Drosyn, optimide)	*Children and adults:* *Cycloplegia:* Instil 1-2 drops of 1% solution, may repeat in 5 min. *Mydriasis:* Instil 1-2 drops of 0.5% solution 15-20 min before examination.	*Drops:* 1% w/v. *Adverse events*: Tachycardia, drowsiness, headache, dry mouth, blurred vision, photophobia.
Tubocurarine	*Neonates:* Start 0.3 mg/k, maintenance 0.1 mg/kg/dose. *Children:* 0.2-0.5 mg/kg start, then 0.04-0.1 mg/kg/dose maintenance. *Adults:* start 6-9 mg, then 3-4.5 mg maintenance.	*Adverse events:* Hypotension, prolonged respiratory depression.
Urokinase (Dabunase, urokinase)	Neonates, infants, children and adults: IV load 4400 units/kg, maintenance dose 4000-10,000 units/kg/hour. *Occluded IV catheter:* Fill entire volume of catheter with urokinase 5000 units/ml and leave in lumen for 1-4 hr.	*Injection:* 2,50,000 iu, 5,00,000 iu/ml. *Adverse events*: Bleeding, hematoma, allergic reactions, bronchospasm
Valproic acid (Valparin, epilex, Encorate-IV preparation)	*Neonates:* Refractory seizures: Load 20 mg/kg orally. Then 10 mg/kg/dose every 12 hr. *Children and adults:* *Seizures:* 10-15 mg/kg/day in 3 doses, then increase weekly by 5-10 mg/kg/day to effect or therapeutic levels.	*Tablet:* 200 mg, 300 mg, 500 mg. *Syrup:* 200 mg/5 ml. *Adverse events*: Drowsiness, irritability, tremor, hearing loss, hepatotoxicity, pancreatitis, diarrhea, vomiting.
Vancomycin (Vancocin, vancogen)	Neonates; postnatal age ≤ 7 days, < 1200 g: 15 mg/kg/day IV q 24 h; 1200-2000 g: 15 mg/kg/day divided q 12-18 h; >2000 g: 30 mg/kg/day IV divided q 12 h; postnatal age > 7 days, <1200 g: 15 mg/kg/day q 24 h; 1200-2000 g: 15 mg/kg/day divided q 8-12 h; >2000 g: 45 mg/kg/day IV divided q 8 h. *Children*: 45-60 mg/kg/day IV divided q 8-12 h; oral dosing for antibiotic-associated enterocolitis; 40-50 mg/kg/day PO divided q 6-8 h. *Adults:* 0.5-1 g IV q 12 h.	*Injection:* 500 mg/ml. *Capsule:* 125 mg. *Adverse events*: Ototoxicity, nephrotoxicity, red-man syndrome.
Varicella-zoster immune globulin, VZIG (Varitect)	Infants born within 5 days of onset of maternal varicella: 125 U IM *Children and adults:* 1 vial (125 units) for every 10 kg body weight (maximum: 5 vials (625 units)	*Injection:* 125 unit vials
Vasopressin (Pitessin, Vasopin)	*Children:* *Diabetes insipidus:* IM, SC 2.5-10 units/dose 2-4 times a day. *GI hemorrhage:* IV continuous infusion 0.002-0.01 units/kg/min. *Adults:* *Diabetes insipidus:* IM, SC 5-10 units/dose 2-4 times/day. *GI Hemorrhage:* IV continuous infusion 0.2-0.4 units/min. *Ampoule:* 20 IU/ml	*Adverse events:* Hypertension, arrhythmias, bradycardia, water intoxication, tremor, circumoral pallor, vomiting.
Vecuronium (Norcuron)	*Neonates:* 0.03-0.15 mg/kg/dose every 1-2 hr as needed. *Children and adults:* 0.05-0.1 mg/kg every hour as needed. *Continuous infusion:* 0.06-0.1 mg/kg/hr. *Ampoule:* 4 mg *Vial:* 4 mg/2 ml	*Adverse events:* Tachycardia, hypotension, bradycardia, hypersensitivity reactions.
Voriconazole	*Adult dose:* Loading dose 6 mg/kg IV q 12 hr followed by 3-4 mg/kg IV q 12 hr: Oral 200 mg q 12 hr then 100 mg q 12 hr	Hepatitis, rash, nausea
Warfarin (Coumadin) (Acitrom, uniwarfin, warf-1)	*Children:* Initial dose 0.2 mg/kg once PO then usual dose approximates 0.1 mg/kg/day PO. Dose titrated to desired PT and INR targets.	*Tablets:* 1, 2, 4, 5 mg *Adverse events:* Bleeding, skin necrosis, hemoptysis.

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Zafirlukast (Accolate)	*Adolescent/adult:* 40 mg/day PO divided q 12 hr	*Tablet:* 20 mg *Adverse events:* Headache, elevated liver function tests.
Zinc chloride	See zinc sulfate	*Injection:* 1 mg Zn/ml
Zinc sulphate (Zevit cap, zincolak, ulseel cap, zincovit)	Deficiency oral *Infants and Children:* 0.5-1 mg/kg/day in 1-3 doses. *Adults:* 25-50 mg/dose 3/times day. *TPN supplement:* *Preterm infants:* 400 µg/kg/day. *Infants < 3 months:* 250 µg/kg/day. *Infants > 3 months:* 100 µg/kg/day. *Children:* 50 µg/kg/day.	*Capsules:* 61.8 mg, 220 mg *Injection:* 1and 5 mg Zn/ml *Syrup:* 10 mg/5 ml *Tablet:* 50 mg *Adverse events:* May cause copper deficiency

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Practical Approach to
PEDIATRIC INTENSIVE CARE

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